University of Alberta

AN ACTIVE-QUIESCENT MODEL FOR THE RADIATION TREATMENT OF CANCER AND ANALYSIS OF PROSTATE CANCER DATA

by

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Abstract

Mathematical modeling is a tool in predicting tumour growth, cancer spread, and the effectiveness of a specific treatment. In this thesis I derive, from first principles, a model for the radiation treatment of cancer which includes the effects of the cell cycle. I divide a malignant cell population into two compartments based on radiation sensitivities. The active compartment includes the four phases of the cell cycle, while the quiescent compartment consists of the G_0 state. Analysis of this active-quiescent radiation model leads to a new interpretation of the α/β ratio of the linear quadratic model. I rewrite the active-quiescent model as a nonlinear birth-death process in order to derive an explicit expression for a tumour control probability (TCP). Finally, I perform preliminary analysis on prostate cancer data obtained from the Cross Cancer Institute. I fit this data to a published deterministic model and critically analyze this model.

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Chapter 1

Introduction

Cancer is a serious disease that affects millions of people worldwide. According to the World Health Organization, 12.5 percent of total deaths every year worldwide are caused by cancer. Also, in 30 percent of these cases, the patients could have been cured had they received early diagnosis and effective treatment. Time and cost are two factors that limit the number of patients eligible to receive early treatment. For these reasons, mathematical modeling is a helpful tool in not only predicting tumour growth and cancer spread, but also in determining the effectiveness of a specific treatment.

One of the common therapies used to treat cancer is external beam radiotherapy. This treatment works by transferring energy to a cell, which causes structural damage that affects cell viability.

Our main objective in this work is to derive a biologically realistic model for the radiation treatment of cancer, that can be used to predict the outcome of a given treatment schedule.

The most widely used mathematical model of the radiation treatment of cancer is the linear quadratic (LQ) model, which predicts the surviving fraction of clonogens after a treatment of dose D is applied to a tumour. This model, in its basic form, assumes that the tumour cell population is uniform, and that the effect of the treatment is independent of the cell cycle. We believe that this is an oversimplification, which prevents complete understanding of the system dynamics. Radiation has a more severe effect on cells that proliferate rapidly. We incorporate this information into our model by dividing the cell population into two compartments: active and resting. We investigate the effects of the cell cycle parameters on our model by performing perturbation analysis. This analysis provides insight on the role the cell cycle has on the effectiveness of the radiation treatment. We are then able to compare the parameters in our cell cycle model with the parameters of the LQ model, which are hypothesized to correlate with the cell cycle. Also, we rewrite our cell cycle model as a birth-death process in order to derive the tumour control

probability (TCP) of the system. The TCP is used to predict the results of a specific treatment, as well as to compare different treatment regimens.

This thesis is divided into five chapters. In Chapter 2, we give some basic cancer cell biology definitions and information in order to have a better understanding of the mechanisms of the disease. In Chapter 3, we review various formulations of both the LQ model, and the TCP, two of the most widely used models for the radiation treatment of cancer. In Chapter 4, we derive a mathematical model of the radiation treatment of cancer that includes active and quiescent cell phase dynamics. This model is formulated as a system of two ordinary differential equations (ODEs). In Chapter 5, we perform linear analysis on the model, as well as perturbation analysis, and find how the model parameters affect solutions. In Chapter 6, we write the cell cycle model as a birth-death process, and use this system to derive the TCP, which generalizes Zaider and Minerbos [29] TCP formulation to a non-uniform cell population . As a preliminary step to the application of the active-quiescent model to the specific case of prostate cancer, in Chapter 7, we discuss the effects of radiotherapy treatment on prostate-specific antigen (PSA) levels in prostate cancer patients. We also summarize the data-fitting work we did in order to determine the validity of a PSA model previously presented. In the final chapter, Chapter 8, we present a discussion of our work, and discuss possible future work.

Chapter 2

Cancer Cell Biology

In the study of cancer, it is important to have a basic understanding of the biological mechanisms that drive the disease. In the following sections, some important features of cancer cells are discussed, including the cell cycle; a basic cancer cell definition; how cancer cells differ from normal cells; and how radiation affects these cells.

It is also important to be familiar with general cancer terminology. We begin by stating that oncology is the study of malignant tumours, where malignant is equivalent to transformed, cancerous, and neoplastic.

Cancer is the result of multiple genetic mutations in genes that are directly involved with the cell cycle progression, differentiation, or apoptosis. For this reason it is important to understand the cell cycle, and its driving factors.

2.1 The Cell Cycle

The cell cycle, as shown in Figure 2.1, can be split into four phases, where the culmination occurs when the cell divides and two daughter cells are formed. Although not considered part of the cell cycle, it is also important to recognize that there is a resting phase G_0 that cells may enter. We think that the G_0 phase is very important when modelling radiation treatment of cancer because the cell is less sensitive to radiation when in this phase.

2.1.1 Cell Cycle Phases [16], [17]

G_1 Phase

This phase is known as gap 1 phase. It occurs just after the cell has split, but must not be mistaken for the resting phase G_0. During this phase, the cell begins to manufacture more proteins in preparation for division. It also experiences other growth: metabolism increases, RNA synthesis is elevated, organelles duplicate. This phase

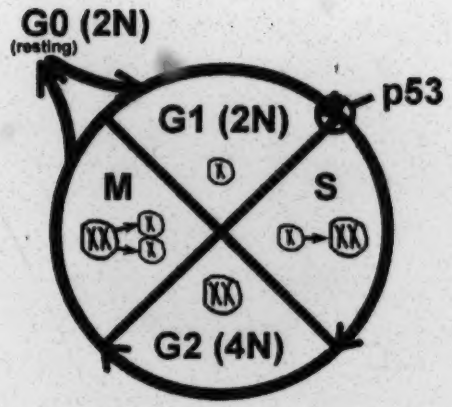

Figure 2.1: Schematic of the cell cycle, including the G_0 phase.

lasts about 18 to 30 hours.

S Phase

This phase is known as the stationary phase, although a cell in the S phase is biologically active. During the S phase, the DNA is copied so that when the cell divides, both cells will have a copy of this genetic information (Note: in human cells, all two meters of DNA are copied!). This phase lasts about 18 to 20 hours.

G_2 Phase

The gap 2 phase occurs just before the cell begins to divide into two cells, and is a preparation stage for this chromosome duplication. Initially, in the gap 2 phase, there is an increase in protein and RNA synthesis. This phase lasts about 2 to 10 hours.

M Phase

This phase is the mitotic phase, where the cell division occurs and two new cells are formed. The chromosomes are first lined up and pulled to either end of the cell, the membrane is pinched together, and two daughter cells are formed. This phase lasts about 30 to 60 minutes.

G_0 Phase

This phase is called the resting phase. During this phase of inaction, cells have not begun to divide. This period of inaction can last anywhere from a few hours up

to a lifetime, and is the phase with the most variable time frame. Once the cell is signalled to reproduce, it then moves into the G_1 phase. Most stem cells found in normal tissues are in the G_0 phase, and are not committed to division.

Phase Determination

A cell's current location in the cell cycle, or current phase, can be determined by identifying which genes are currently active [20]. Also, we note that the time required to complete an entire cell cycle is called the generation time.

2.1.2 Cell Cycle Checkpoints [17]

During the cell cycle, there are three main checkpoints. At these checkpoints, a decision is made to either stop the events, or to continue depending on the assessment of the condition of the DNA, as well as the events succession. If DNA damage is detected, then events are stopped so that the cell can repair the damage. However, if the damage is severe, the cell will undergo apoptosis (programmed cell death).

G_1 Checkpoint (restriction point)

After cell division, the new daughter cells enter this checkpoint. If a cell is big enough, and the environment is suitable, then the cell may proceed directly to G_1. If the cell fails at this check it moves into G_0 (where most of the cells in our body are found). This checkpoint is the most important of the three.

It is important to note that before this restriction point, the cell depends on external growth factors to progress through G_1. After the restriction point, the cell is independent of external factors.

G_2 Checkpoint

If the DNA replicated properly, the cells are big enough, and the environment is suitable, then the cell may proceed. (And if not, reparation takes places.)

Metaphase Checkpoint

If the chromosomes are aligned on the spindle correctly, the cell may proceed.

The development of normal, healthy cells is a very tightly controlled system of division, growth, and death. In the case that this control system fails, normal development ceases to occur. When this cycle is uncontrolled, cells created form a mass which is a tumour.

2.2 Cancer Cells

Cancer arises when multiple growth control gene changes occur in a single cell. These changes cause the cancer cell to either ignore, or override a regulating factor of mitosis. Once this single cell is transformed, cancer cells are produced as this cell passes through uncontrolled, repeated mitosis. The mass of cancer cells produced forms the tumour. As the tumour grows, it starts to release proteins that promote blood vessel growth to and within the tumour. This process is called angiogenesis. When angiogenesis begins to take place, the tumour will be composed of about one million cancer cells.

It is important to note the difference between benign tumours and malignant tumours. A benign tumour is one that does not spread or metastasize to other parts of the body (tumour cells remain at the original site). A malignant tumour is one that contains cells that signal the blood vessel formation at the site. By doing this, the cells have a source of food and oxygen, as well as a route to other parts of the body (via the bloodstream or lymphatic system). The cells that leave the original site through the newly formed vessels and latch on to another site form new tumours that are biologically identical to the first. This is what we call metastasis. Cancer cells can also move through tissue, without blood or lymphatic vessels [8].

There are two main groups of cancer genes: oncogenes and tumour suppressor genes (TSG) [16], [17].

2.2.1 Oncogenes

Oncogenes are mutated genes which code for proteins which are involved in cell cycle regulation. This means they control the growth of cells by pushing the cell through different paths. Genes that are potentially oncogenes (same genes but without mutation), are known as proto-oncogenes. These proto-oncogenes become cancerous for many different reasons: over or under expression, inactivation, differing substrates, and different affinity for substrate.

2.2.2 Tumor Suppressor Genes

Tumour suppressor genes, in their unaltered healthy state, restrict growth. They are inactivated during tumourigenesis, which leaves them unable to inhibit growth as per usual. An example of a tumour suppressor gene is the p53 protein. This protein inspects the DNA and when it discovers DNA that is damaged, it halts the chromosome duplication process and activates the DNA repair systems. If the DNA damage takes too long to repair, the p53 protein causes apoptosis. (More than 50 percent of all cancers have a disabled p53 gene.)

2.2.3 Effect on Cell Cycle

In cancer cells, control of the cell cycle can be lost in two ways. The cells can be signalled to divide continuously, so that they never enter the resting phase of the cell cycle, or a signal that would normally tell the cell to cease division may have been removed.

When a new cancer cell is formed, if it is detected early enough by the immune system, it will be destroyed. If it avoids detection, it begins division so a tumour can be established (a mass of cells that is difficult for the body to annihilate).

2.3 Cancerous and Normal Cell Differences

Although cancer cells do still progress through the same cell cycle as healthy cells, these transformed cells exhibit abnormal growth patterns due to multiple genetic mutations.

Cell Death
Tumour cells have no program for cell death. They are thought to be immortal, and will proliferate indefinitely in culture, with the right nutrients.

Hayflick Limit
Tumour cells have no limit on the number of cell divisions.

Serum Dependence
Tumour cells have a lower serum dependence than healthy cells. It has been demonstrated that tumour cells secrete their own growth factors.

Differentiation
Tumour cells don't completely differentiate. Healthy cells become specialized cells suited for specific functions throughout the body, or make products usually associated with less differentiated states.

Contact Inhibition
Tumour cells have no contact inhibition of density dependence. The loss of contact inhibition can be detected by observing the formation foci of rounded cells or overlapping cells within the regular pattern of normal surrounding cells.

Anchorage Dependence
Tumour cells are anchorage independent. Instead of sticking to their neighbouring cells, cancer cells tend to "round up" and break attachments. The neighbour cells surface modification account for many of the properties associated with transformed cells. Proteins are lost from the cell surface and cause a decrease in cell adhesion. This leads to loss of density dependent growth and disorganized

growth patterns. Altered cell surfaces also facilitate detachment from tissue in turn making metastases possible (cells can migrate to other parts of the body).

Tumourigenesis
Tumourigenesis is the formation of invasive or metastatizing tumours in a living host animal.

Proteolytic Enzyme Production
The breakdown of tissue barriers is accomplished by the large quantity of secreted enzymes, which is important for metastasis.

Angiogenesis Factor
Tumour cells release factors capable of inducing blood vessel formation to the tumour.

Nutrient Requirement
Nutrient requirements are lower than that of normal, healthy cells.

Abnormal Karyotype (genetic material make-up)
Cancerous cells may have an abnormal number of chromosomes, or chromosomes with abnormal structures such as translocations, deletions, duplications, or inversions [16]. A translocation describes a chromosome that has gained an end of another chromosome. Deletions and duplications describe instances where a section of DNA is either missing, or duplicated. An inversion occurs when a segment of a chromosome, is broken free, rotated 180 degrees, and returned to its original position in the same chromosome. If mutation in a critical cell cycle protein occurs, the cells will not be able to progress through the cell cycle as they normally would.

2.4 Radiation Treatment of Cancer

Radiation therapy works to treat cancer by attacking reproducing cancer cells, but also inadvertently affects the normal, healthy cells that are proliferating. This damage to normal cells is the cause of side effects. Every time radiotherapy is given there must be a balance between attacking cancer cells and avoiding destruction of healthy cells.

Radiation can be simply described as energy that is carried by waves or streams of particles. The key aspect in using this energy to treat cancer is that radiation has the capability of altering genetic material in a cell. As seen above, this genetic code controls cell growth and proliferation. For this reason, it is important to fully understand the cell cycle in order to understand how radiation is used as a treatment.

2.4.1 Radiation and the Cell Cycle

Radiation is more effective on cells that are active and dividing quickly, while it is much less effective on cells that are in the G_0 resting phase, as well as on cells that divide slowly [20]. The term radiosensitivity is used to describe how sensitive a cell is to radiation damage.

Genotoxic agents are chemicals, such as those produced by radiation therapy, capable of causing damage to DNA. When cells are exposed to genotoxic agents several checkpoints are triggered. A cell that has suffered DNA damage will not enter into the S phase, thus avoiding damaged DNA from being replicated. This prevents fixation of mutations in the DNA of the daughter cells during replication. Also, if the damage to the DNA is not repairable, or takes too long to repair, the p53 protein will cause the cell to self-destruct through apoptosis.

When chromosomes are damaged as a result of genotoxic agents, cells will not enter mitosis until the damaged chromosomes are repaired. Normal, healthy cells will respond to this DNA damage by inducing both a G_1 and a G_2 arrest. For both processes the tumour suppressor gene p53 is crucial. Those cells that have a malfunctional p53 protein are unable to induce cell cycle arrest after DNA damage. These unarrested cells quickly accumulate more mutations every time division occurs [16].

2.4.2 Effects of Ionizing Radiation

Ionizing radiation causes ionization, which is the loss of an electron in atoms or molecules. When an electron is lost, energy is transferred, and this energy disrupts chemical bonds, resulting in ionization. These ionizations, when induced by radiation, can act directly on molecules forming cellular components, or indirectly on water molecules. When acting on water, the ionizations cause water-derived radicals (highly reactive molecules that can bind to and destroy cellular components). These radicals quickly react with molecules near them, and this results in chemical bond breakage or oxidation of the affected molecules. In cells, there are a variety of possible radiation induced lesions, although the most harmful to the cell are the lesions which effect the DNA structure.

DNA occurs in pairs of complementary strands, and radiation can induce single strand breaks, or double strand breaks. Single strand breaks are the more common lesion of the two, and can usually be repaired by the cell (undamaged strand serves as template for production of complementary strand). Double strand breaks are caused by either a single event which severs both DNA strands, or by two independent single strand break events close in time and space. Double strand breaks are considered more harmful than single strand breaks, as they are difficult to repair. Even when repair is attempted, broken ends may be joined together, leading to mis-

repairs. These misrepairs cause mutations, aberrations (of chromosomes), or cell death.

Deletion of DNA segments is the most common form of radiation damage in cells that survive radiation treatment. The deletion may be caused by the misrepair of two separate double strand breaks in a DNA molecule by joining of the two outer ends and loss of the section between the breaks. However, it may also be a result of the cleaning process, where enzymes digest nucleotides (component molecules of DNA) of the broken ends prior to rejoining them to repair a single double strand break [17].

2.4.3 High-LET and Low-LET Radiation

Radiations differ by their constituents (electrons, protons, neutrons, etc.), but also by their energy. Radiations that cause dense ionization along their track are called high-linear-energy-transfer (high-LET) radiation (such as proton beams), which represents a physical parameter to describe average energy released per unit length of the track. Low-LET radiations (such as X-ray or electron beams) produce ionizations more sparsely along their track and so the energy deposits are more evenly distributed within a cell.

Radiation dose is the amount of energy per unit of biological material, and is measured in grays (Gy). One gray is defined as the absorption of one joule of radiation energy by one kilogram of matter.

High-LET radiations are more destructive to biological material than low-LET radiations. This is because at the same dose, the low-LET radiations cause the same number of radicals to be more evenly distributed within a cell, while high-LET radiations transfer most of their energy to a small region of the cell. The localized DNA damage caused by many ionizations in a small region of a cell from high-LET radiation is more difficult to repair than the more diffuse DNA damage caused by the ionizations from low-LET radiations.

Chapter 3

Review of the LQ Model and the TCP

3.1 The Linear Quadratic Model

The linear quadratic model (LQ model) is the most common cell survival formalism used when modelling radiation treatment of tumours. This LQ expression was originally used by Sinclair in 1966 [23], who found that an expression of this form fit the cell survival data he analysed, although he could not biologically justify this discovery. The model determines the surviving fraction of cells after radiation of a specified dose, where a cell survives the dose application if it is able to act as a progenitor for significant line of offspring. (The operational definition commonly used for cell survival is that a cell survives if it produces at least 50 offspring.) The LQ formula is written as $S(D) = e^{\alpha D + \beta D^2}$, where $S(D)$ is the surviving fraction of cells after application of dose D, and α and β are the model parameters. Shortly after this LQ expression was proposed, others began to investigate the biological meaning of this expression.

In 1971, Kellerer and Rossi [11], who are now recognized as pioneers of radiobiology and radiation chemistry, published the two-step model of radiation action, which maintained the LQ form. In this model, they considered cells to have complex target sites which were impaired by a dual lesion. These lesions resulted from energy deposits via two charged particles, or instantaneously by one charged particle. These charged particle energy deposition events were considered to be statistically independent discrete events. The two-step inactivation process they described is depicted in Figure 3.1, where state 1 is no damage, state 2 is predamage, and state 3 is damage, or dual lesion effect.

The system of differential equations that governs the behaviour of this process has a solution that can be expressed as a power series, where the coefficients are composed of transition frequencies between states. The solution of interest in this case is the component which is equal to the effect probability, or the fraction of objects in state 3 at absorbed dose D. This effect probability for the two-step scheme

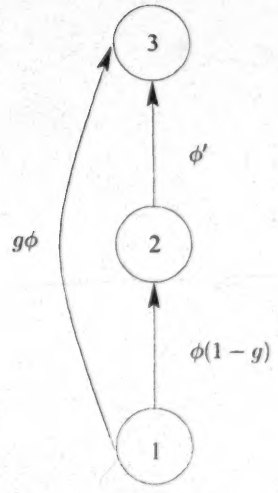

Figure 3.1: The Kellerer and Rossi two-step inactivation process. State 1 is no damage, state 2 is predamage, and state 3 is damage. The frequency of events which affect the undamaged site is given by ϕ; the fraction of events which cause a dual lesion instantaneously is given by g; and the frequency of events which cause damage to a cell in the predamage state is denoted ϕ'.

is:

$$E(D) = g\phi D + \frac{\phi^2}{2}D^2$$

assuming that g is small relative to 1, or equivalently, that instantaneous double lesions are less likely to occur than two event double lesions.

Kellerer and Rossi speculated that the damaging effects of radiation were chromosome aberrations, which was consistent with their model, as well as the idea that a site is composed of aligned, small, string-like targets.

The subsequent endeavor to justify the LQ model was by Chadwick and Leenhouts, in 1973 [5]. The process they described is similar to the two-step scheme of Kellerer and Rossi, although Chadwick and Leenhouts asserted that the primary action of radiation is molecular bond breakage, where the molecule affected is DNA. The DNA is damaged by double strand breaks, which can occur either in one radiation event, or in two independent radiation events, referred to as single strand breaks. After a cell sustains a number of double strand breaks, it will no longer have the ability to proliferate. Another assumption made by Chadwick and Leenhouts was that it is possible for these broken bonds to be repaired. The LQ model $S(D) = e^{\alpha D + \beta D^2}$ was derived using these assumptions, and the parameters α and β which appear in the exponent implicitly accounted for various factors which affected cell survival, such as the cell cycle. In 1968, Sinclair [24] declared that a sig-

nificant shortcoming of the available hit and target models was that they assumed cell populations to be homogenous, meaning that radiation sensitivity in the cell cycle was ignored. Chadwick and Leenhouts demonstrated that the LQ model had the ability to incorporate these cell cycle effects, by allowing α to vary throughout the cell cycle.

Another individual who made a significant contribution in radiobiology was Barendsen [1]. In the late 1960s, Barendsen examined cell survival curve characteristics for different dose distributions and radiation qualities, without making use of a model to describe these curves. In 1982, Barendsen [1] published a paper in which he developed a model that included fractionation effects. This model assumed that cell survival is given by the LQ formalism, although Barendsen rejected all previously suggested hypotheses on the basis that they failed to adequately predict cellular damage as a function of dose, dose fractionation, and radiation quality. He did claim, however, that the LQ formalism could be employed without having a specific mechanism of action in mind. In order to include fractionation effects, Barendsen maintained the assumption that lesion production occurs either instantaneously, or in two steps, as a result of interacting sub-lethal lesions, although he added the restriction that these sub-lethal lesions lose their capacity to interact with one another exponentially. Also, he assumed that the cell cycle is irrelevant to the sensitivity of the cells, so all fractions are equally effective. If n is the number of fractions, and D is the dose per fraction, then the number of lethal lesions to a single cell after dose D, denoted by F, is given by:

$$F(D) = -\alpha D(1 + \beta/\alpha \cdot D/n).$$

Assuming that the lesions are uniformly distributed throughout cells, the survival probability of cells is given by

$$S(D)/S(0) = e^{-\alpha D(1+\beta/\alpha \cdot D/n)}.$$

Although the LQ model seemed to confirm experimental results, the absence of a treatment time factor prevented universal acceptance. However, in the late 1970s, cell kineticists found that different tissues react at different rates after irradiation. Tissues in which cell proliferation is slow exhibit a late response to treatment, whereas tissues whose cell populations have a faster turnover respond acutely to treatment. This difference in response has been attributed to the fact that a cells' sensitivity to radiation depends on a cells proliferation rate. In the model we present in Chapter 3, we incorporate this idea that the effects of radiation are cell phase dependent by considering a cell population divided into two compartments of different sensitivities. The remaining healthy cells in the population respond to cell damage or death by compensatory increased regeneration, which means they temporarily increase their proliferation rate. Classically, the application of the LQ model was

to minimize the radiation damage of late-reacting tissues, or the healthy tissues surrounding the tumour. In this classical application, the standard LQ model suffices since the compensatory cell response occurs sometime after the treatment. In the case of early-reacting tissues, however, the compensatory proliferation occurs during treatment, and must be included in the model so that the cell killing is not overestimated. To incorporate the time factor, the surviving fraction can be multiplied by a reproduction factor as follows:

$$S(D) = e^{-(\alpha D+\beta D^2)+\gamma(T-T_k)},$$

where

- T is total time considered,
- T_k is the time at which cell regeneration begins, and
- γ is the regeneration rate.

In [3], Buffa, Fenwick and Nahum present a variation of the LQ model which includes the effects of sensitivity variations within the tumour, although it was thought to be of less importance then the variability of radiosensitivity over the population. Suppose that the sensitivity within a tumour is Gaussian distributed with variance σ_{int}. This leads to the following survival fraction:

$$S(D) = e^{-\alpha D\left(1+\frac{\beta}{\alpha}\cdot\frac{D}{n}+\frac{1}{2}\cdot\frac{\sigma_{int}^2}{\alpha}\cdot G(w)D\right)}$$

where G is the Lea-Catcheside factor, and w is the sensitivity redistribution time and inherently contains information on the length of the cell cycle. Below we give a simple derivation of the LQ model, including the generalized Lea-Catcheside factor, found in [21], and then later adapted in [22]. This derivation uses the LQ model to approximate the Lethal Potentially Lethal (LPL) model, and is one of many attempts to mechanistically justify the LQ model.

To begin the derivation, we must be familiar with the LPL model. This model looks at DSB production, restitution, and binary misrepair in order to determine per cell averages of both potentially lethal (PL) and lethal (L) lesions.

Assume that a tumour formed of a non-cycling, uniform group of cells is irradiated. The total accumulated dose at time t is given by $D(t)$, and the radiation dose rate is given by $R(t) \equiv \frac{dD}{dt}$. Also, assume that the most significant radiation damage is DNA double strand breaks (DSBs). After a DSB occurs, it is usually repaired within a half hour, but could be misrepaired. If a misrepair occurs, this could cause cell death at the next mitosis. Per unit dose, the average number of DSBs produced is δ. Most of these DSB lesions are restituted, which means that broken pieces of a DSB are rejoined, though not necessarily correctly. The restitution rate constant is denoted by λ. Some DSB that do not undergo restitution, undergo binary misrepair. Binary misrepair involves two chromosomes, each having suffered a DSB,

rejoining to each other. The result can be either a dicentric, which describes a chromosome that contains two centromeres, or a translocation. Dicentrics are usually lethal, whereas translocations can cause phenotype changes, and sometimes have serious implications, however they are not considered lethal. The binary misrepair rate constant is κ. If we denote the average number of DSB per cell as $U(t)$, then the first equation in the LPL model is given by

$$\frac{dU(t)}{dt} = \delta R - \lambda U - \kappa U^2. \tag{3.1}$$

In equation (3.1), the first term, δR is the average number of DSB produced by irradiation in dt; the second term, λU, is the per cell restitution rate; and the third term, κU^2 represents the binary misrepair rate, under the assumption that we have mass-action chemical kinetics.

Now we consider the number of DSB that will be lethal. Since only a proportion of restitutions are not viable, we denote this proportion by α. Also, only a certain number of binary misrepairs will be lethal, and we denote this proportion by c. The average number of lethal lesions per cell is $L(t)$. The average rate of lethal lesion production per cell is then given by

$$\frac{dL(t)}{dt} = \alpha\lambda U + c\kappa U^2. \tag{3.2}$$

We can now begin the derivation of the LQ model. First, we assume that the term κU^2 in (3.1) is negligible, although this might not be the case in (3.2). Using this assumption, (3.1) reduces to

$$\frac{dU(t)}{dt} = \delta R - \lambda U, \tag{3.3}$$

and can be integrated to obtain

$$U(t) = \delta e^{-\lambda t} g(t) \tag{3.4}$$

where $g(t) = \int_{-\infty}^{t} \dot{D}(s) e^{\lambda s} ds$.

We substitute this result for $U(t)$ in equation (3.2) to obtain

$$\frac{dL(t)}{dt} = \alpha\lambda\delta e^{-\lambda t} g(t) + c\kappa \left(\delta e^{-\lambda t} g(t)\right)^2. \tag{3.5}$$

We integrate (3.5) for all time to determine the total number of lethal lesions produced by the radiation treatment:

$$\int_{-\infty}^{\infty} dL(t) = \alpha\lambda\delta \int_{-\infty}^{\infty} e^{-\lambda t} g(t) dt + c\kappa\delta^2 \int_{-\infty}^{\infty} \left(e^{-\lambda t} g(t)\right)^2 dt. \tag{3.6}$$

First integrate by parts the first term on the right hand side of (3.6) to get

$$\int_{-\infty}^{\infty} e^{-\lambda t} g(t) dt = \left[-\frac{e^{-\lambda t}}{\lambda} g(t) \right]_{-\infty}^{\infty} + \frac{1}{\lambda} \int_{-\infty}^{\infty} \dot{g}(t) e^{-\lambda t} dt \tag{3.7}$$

where $\left[-\frac{e^{-\lambda t}}{\lambda} g(t) \right]_{-\infty}^{\infty}$ is zero because as $t \to \infty$, $e^{-\lambda t} \to 0$ and $g(t)$ is bounded as $t \to \infty$. As $t \to -\infty$, there will be some time t_{birth} such that the dose rate prior to this time is zero, so $R(t_{birth} - t) = 0$, for all t positive. Using this, and the fact that $\dot{g}(t) = \dot{D}(t) e^{\lambda t}$, we have that

$$\begin{aligned} \int_{-\infty}^{\infty} e^{-\lambda t} g(t) dt &= \frac{1}{\lambda} \int_{-\infty}^{\infty} \dot{g}(t) e^{-\lambda t} dt & (3.8) \\ &= \frac{1}{\lambda} \int_{-\infty}^{\infty} \dot{D}(t) e^{\lambda t} e^{-\lambda t} dt & (3.9) \\ &= \frac{1}{\lambda} \int_{-\infty}^{\infty} \dot{D}(t) dt. & (3.10) \end{aligned}$$

Also, we know that $\int_{-\infty}^{\infty} \dot{D}(t) dt = D(\infty)$, so we get

$$\int_{-\infty}^{\infty} e^{\lambda t} g(t) dt = \frac{\delta}{\lambda} D(\infty). \tag{3.11}$$

To calculate the integral of the second term on the right hand side of (3.6), we again perform integration by parts as follows

$$\int_{-\infty}^{\infty} e^{-2\lambda t} g^2(t) dt = \left[-\frac{e^{-2\lambda t}}{2\lambda} g^2(t) \right]_{-\infty}^{\infty} + \frac{1}{\lambda} \int_{-\infty}^{\infty} g(t) \dot{g}(t) e^{-2\lambda t} dt. \tag{3.12}$$

Using the same arguments as above regarding the lifespan of an individual, we have that $\left[-\frac{e^{-2\lambda t}}{2\lambda} g^2(t) \right]_{-\infty}^{\infty} = 0$. This leads to

$$\int_{-\infty}^{\infty} e^{-2\lambda t} g^2(t) dt = \frac{1}{\lambda} \int_{-\infty}^{\infty} g(t) \dot{g}(t) e^{-2\lambda t} dt. \tag{3.13}$$

Simplify to obtain

$$\begin{aligned} \int_{-\infty}^{\infty} e^{-2\lambda t} g^2(t) dt &= \frac{1}{\lambda} \int_{-\infty}^{\infty} \int_{-\infty}^{t} \dot{D}(s) e^{\lambda s} ds \dot{D}(t) e^{-\lambda t} dt & (3.14) \\ &= \frac{1}{\lambda} \int_{-\infty}^{\infty} \int_{-\infty}^{t} \dot{D}(s) e^{\lambda (s-t)} ds \dot{D}(t) dt & (3.15) \\ &= \frac{D^2}{2\lambda} G & (3.16) \end{aligned}$$

where G is the Lea-Catcheside functional

$$G = \frac{2}{D^2}\int_{-\infty}^{\infty}\dot{D}(t)\int_{-\infty}^{t}e^{-\lambda(t-s)}\dot{D}(s)dsdt. \tag{3.17}$$

Now we substitute these results into (3.6) to get

$$\begin{aligned} L(\infty) &= \alpha\lambda\frac{D}{\lambda} + c\kappa\delta^2\frac{D^2}{2\lambda}G & (3.18)\\ &= \alpha D + \frac{c\kappa\delta^2}{2\lambda}D^2G, & (3.19)\end{aligned}$$

which is the LQ Model, with $\alpha = \alpha$, and $\beta = \frac{c\kappa\delta^2}{2\lambda}$.

The LQ model, in its basic form, provides a good approximation of most other ODE models that incorporate the repairable damage component into the tumour cell dynamics, and is a favoured choice due to its simplicity (only two adjustable parameters, α and β).

3.1.1 The α/β Ratio [4]

The ratio of the two adjustable parameters in the LQ model, α and β, has been found to correlate with the cell cycle length. Tissues which have a slow cell cycle are composed of cells which proliferate slowly. These slow cycling tissues correspond with a smaller α/β ratio. Brain tissue and the spinal cord are examples of slow cycling tissues, both of which have an α/β ratio of about 3 Gy. Tissues which have a fast cell cycle are composed of cells that proliferate quickly and are associated with a larger α/β ratio. Most tumours are composed of cells which cycle quickly, and have an α/β ratio of approximately 10 Gy. It is important to note that in radiotherapy, it is usually the case that the slow cycling tissues are those which we are trying to protect.

3.2 TCP Models

The probability that no malignant cells are left in a specified location after irradiation is known as the tumour control probability (TCP). This probability is used to determine an optimal treatment strategy where the dose to the tumour is increased without increasing the damaging effects of radiation of healthy tissues. In this section we discuss several models for the TCP of an irradiated tumour.

The most common and simplest expression for the TCP is one which relies on Poisson statistics. Let D be the total radiation dose, and denote the surviving

fraction of cells after an application of dose D by $S(D)$. Also, assume that the number of tumour cells present prior to the treatment is n, which implies that after treatment, $nS(D)$ cells survive. Define a random variable X which represents the density of cells surviving the treatment, and let X be Poisson distributed. The Poisson distribution is the limiting case of the binomial distribution for $n \to \infty$ where $nS(D) = \lambda = constant$ is true. This condition implies that the number of cells present before treatment, n, is large, and that survival is a rare event. In the case this condition is true, the probability that k cells survive is given by

$$\Pr(X = k) = \frac{\lambda^k e^{-\lambda}}{k!},$$

with expected value λ. Substitute $nS(D)$ for λ to get

$$\Pr(X = k) = \frac{(nS(D))^k e^{-nS(D)}}{k!}.$$

Let $k = 0$, to obtain the probability that no cells survived the treatment, which is the TCP. The expression for the TCP is:

$$\text{TCP} = \Pr(X = 0) = e^{-nS(D)}. \tag{3.20}$$

Expression (3.20) is only valid when the cell survival probability is small, and the number of cells surviving irradiation is much less than the initial number of tumour cells, which are the usual conditions in radiotherapy treatments.

In the following sections we critically discuss some other existing TCP theories. In particular, the model of Zaider and Minerbo is of interest, and we extend their TCP result in chapter 6.

3.3 TCP Model of Niemierko and Goitein

The biophysical model presented by Niemierko and Goitein [19] is a variation of the more general model first described by Goitein, Niemierko, and Okunieff [9]. This pared model contains only five parameters, in order to facilitate data fitting. The assumptions made are that: tumours are composed of non-interacting clonogens; clonogens have varying sensitivities; average tumour sensitivities vary among individuals; and clonogen deaths are considered to be independent events.

Then the surviving fraction of clonogens is estimated using a variation of the LQ Model

$$S(d) = S_2^{\frac{d}{2}\left(\frac{\alpha/\beta + d}{\alpha/\beta + 2}\right)} \tag{3.21}$$

where d is the dose delivered to a clonogen in one fraction, S_2 is the probability of that a clonogen survives a 2 Gy dose, and the parameters α and β are the LQ Model parameters.

Variability in a single parameter, namely S_2, accounts for the varying sensitivities among clonogens in an individual as well as among a population. For individual sensitivity variation, the values S_2^{ind} are assumed to be Gaussian distributed around the tumour mean $\overline{S_2^{ind}}$ with a standard deviation $\sigma_{ind.}$. Similarly, for sensitivities among a population, the values $\overline{S_2^{ind}}$ are assumed to be Gaussian distributed around the population mean $\overline{S_2^{pop}}$ with standard deviation σ_{pop}. The Gaussian probability density functions associated with an individual or a population are denoted by G_{ind} and G_{pop} respectively. The TCP associated with this biophysical model is then given by:

$$TCP = \int G_{pop} TCP_{ind} d\overline{S_2^{ind}}.$$

This expression defines a mean value for the TCP of a population, using the following that the probability of surviving a dose of i Gy is

$$S_i = S_2^{\sum_{k=1}^{n} \frac{d_k}{2}\left(\frac{\alpha/\beta + d_k}{\alpha/\beta + 2}\right)},$$

with mean

$$\overline{S_i} = \int G_{ind} S_i d S_2^{ind}.$$

Also, mean TCP for an individual is given as

$$TCP_{ind} = e^{\left(-NC \sum_{i=1}^{NP} (\nu_i \overline{S_i})\right)}. \tag{3.22}$$

Here,

NP	is the number of dose calculation points,
NC	is the number of clonogens,
ν_i	is the fractional volume associated with dose calculation point i, and
n	is the number of fractions.

This model is useful because it includes the effects of varying radiation sensitivities among clonogens within a tumour, as well as the varying average clonogen sensitivities among individuals in a population. Despite these advantages, the model calculates only an average TCP for the population, and not the TCP for an individual, and is independent of the overall treatment time.

3.4 The TCP Model of Webb and Nahum

The cell density model presented by Webb and Nahum in [27] is an extension of the model first proposed by Nahum and Tait [18]. This model incorporates both non-uniform clonogenic cell density as well as non-uniform dose. In order to do this, consider the tumour to be partitioned into M small volume elements, and the dose and cell density within each of these elements uniform.

The probability that no clonogens survive after the tumour is irradiated by a total dose D, for subvolume j is given by

$$TCP = \prod_{j=1}^{M} e^{-N_{0,j}e^{(-(\alpha D_j + \beta D_j^2))}} \tag{3.23}$$

where the initial number of clonogens in the j-th volume element is defined as $N_{0,j} = \rho_j V f_j$, and ρ_j is the clonogen density of element j, V is the total tumour volume in cm^3, and f_j is the fractional volume of element j. In Ebert and Hoban [12], each subvolume consists of cells with different sensitivities. In this case, the TCP is dominated by the smaller values of $\alpha_j D_j$, or the subvolumes of lower sensitivity. These lower sensitivity subvolumes have a substantial effect on the tumour response to radiotherapy, and at low doses the TCP is close to zero in these regions.

This model is useful due to its inclusion of the effects of an inhomogeneous tumour. However, this model depends only on the total dose of radiation administered, and therefore has no time dependence. This means that despite the treatment regimen, if the total dose applied is the same, the TCP will also be identical. This model could be improved by including the effects of a time dependent dose function.

3.5 Zaider and Minerbo

A birth-death model earlier described by Kendall in [13], is applied to the radiation treatment of cancer by Zaider and Minerbo [29]. This birth-death process can be solved to obtain an expression for the TCP, which satisfies $TCP(t) = P_0(t)$ where $P_i(t)$ is the probability that i clonogens are alive at time t. In this model, the cell birth rate is denoted by b, and the cell death rate is denoted by δ. The death rate δ is composed of the sum of two components: death due to radiation, $h(t)$, and radiation-independent death, d. The radiation death term $h(t)$ is known as the hazard rate, and in the case of the LQ survival probability, is $h(D(t)) = (\alpha + 2\beta D)\dot{D}$. The equation for $P_i(t)$, written in differential form, for $i \geq 1$, is

$$\frac{dP_i}{dt} = (i-1)bP_{i-1}(t) - i(b+\delta)P_i(t) + (i+1)\delta P_{i+1}. \tag{3.24}$$

In (3.24), the first term refers to the probability of gain of one clonogen, the second term refers to the probability of no change in number of clonogens, and the third term refers to the probability of loss of one clonogen. These three cases represent all possible events that can occur in a small time interval.

Equation (3.24) is solved using a generating function $A(s,t)$, and in particular, $TCP(t) = A(s=0,t)$. The expression obtained for the TCP is as follows:

$$TCP(t) = \left[1 - \frac{S(t)e^{(b-d)t}}{1 + bS(t)e^{(b-d)t}\int_0^t \frac{dt'}{S(t')e^{(b-d)t}}}\right]^n \tag{3.25}$$

where $S(D)$ is the survival probability, usually taken to be the the LQ model.

Model (3.25) is perhaps the most intuitive model discussed here, while still including effects of a time varying dose rate and a radiation-dependent death rate component. This model could be extended by including the effects of varying sensitivities within a tumour, and we do this in Chapters 4 through 6.

3.6 Other Variations

As well as obtaining expressions for the TCP, recent studies also look at expressions for the NTCP, or Normal Tissue Complication Probability. This NTCP quantifies the undesirable effects experienced by the patient due to the radiation treatment. Using both TCP and NTCP expressions simultaneously is beneficial in planning safer, but still effective treatment regimes.

Chapter 4

Derivation of an Active-Quiescent Radiation Model

In this chapter, we derive a model for the radiation treatment of cancer cells that includes active and quiescent cell phases. The derivation begins from first principles, at the microscopic level by considering target sites inside a cell that can potentially be damaged by radiation. A target site is damaged when an energy deposition via radiation occurs at that site, which we model as stochastic events. Based on this information, we can describe the effects of radiation on the cellular level. The model includes a quiescent state, G_0, and an active state, which combines G_1, S, G_2 and M-phases. In Chapter 5, we then perform linear analysis, followed by perturbation analysis in order to investigate the model dynamics. We also obtain an interpretation of the model parameters so they can be compared to the LQ model parameters.

4.1 Derivation of an Active-Quiescent Radiation Model from First Principles

Radiation causes ionizing charged particles to deposit energy in discrete regions along the track they travel. We will call a single energy deposition event a single-hit event, and in the case where a region is hit twice within a sufficiently small time interval, we call this a two-hit event. We also assume that all events are stochastically independent [11].

We split the model derivation into five steps. In Step 1, we look at a single cell, and define the probabilities that this cell is damaged by radiation. In Step 2, we look at a group of cells, but split this group into two compartments, active and quiescent, and apply the results from Step 1 to each compartment. In Step 3, we use radiation physics to derive expressions for the damage probabilities. In Step 4, we derive the radiation induced death rates for both cell compartments. Lastly, in Step 5 we use

these derived death rates in an ODE model.

Step 1: One Cell

Consider a single cell, which contains specific sites, called active sites, that are susceptible to radiation damage.

Assume that a single cell has n active sites, labelled $d_1, d_2, \ldots, d_m, \ldots, d_n$, where $d_i, i = 1, \ldots, m$ need two hits to be damaged, and $d_i, i = m+1, \ldots, n$ need only one hit to be damaged.

We consider radiation of energy E. We define $P_{H,i}$ as the probability that radiation with energy E causes the site d_i to experience a single-hit event in a given unit of time Δt. Similarly, we define $P_{2H,i}$ as the probability that radiation with energy E causes the site d_i to experience a two-hit event in a given unit of time Δt. We expect these two probabilities to be related, due to the fact that a two-hit event consists of two separate single-hit events, close in both time and space (see Step 3).

More explicitly,

$$\begin{aligned}\text{Prob(single hit at } d_i) &= P_{H,i} \\ \text{Prob(two hits at } d_i) &= P_{2H,i}.\end{aligned}$$

Next, we compute the probability that at least one site experiences a single-hit event. Any of the n sites susceptible to radiation damage can experience a single-hit event. For sites 1 to n,

$$\begin{aligned}&\text{Prob (at least one of the } d_i \text{ experiences a single hit)} \\ &= 1 - \text{Prob (none of the } d_i \text{ experiences a single hit)} \\ &= 1 - \prod_{i=1}^{n}(1 - P_{H,i}).\end{aligned} \tag{4.1}$$

Similarly, we compute the probability that at least one site experiences a two-hit event, where only the sites susceptible to two-hit damage need to be considered here. For sites 1 to m,

$$\begin{aligned}&\text{Prob (at least one of the } d_i \text{ experiences a two-hit event)} \\ &= 1 - \text{Prob (none of the } d_i \text{experiences a two-hit event)} \\ &= 1 - \prod_{i=1}^{m}(1 - P_{2H,i}).\end{aligned} \tag{4.2}$$

Step 2: Many Cells

Consider a group of cells, where each cell has an associated number of active sites susceptible to single-hit damage and two-hit damage respectively. We investigate the probabilities that the k-th cell dies after a single-hit, or a two-hit event, where cell death is defined as a cell that produces less than 50 offspring.

At this point, we discern between active and quiescent cells. We separate cells into these two compartments, where the active compartment includes the cell cycle phases G_1, S, G_2, M, and the quiescent compartment includes only G_0. We denote the active cells by $u_i, i = 1, \ldots, p$, and the quiescent cells by $q_i, i = 1, \ldots, r$.

We assume that two-hit events, more commonly called double strand breaks (DSB), play a minor role for the quiescent cells, and that when these cells do receive a DSB they have a good chance of repairing this lesion. Hence we assume that quiescent cell death due to two-hit events is negligible. The active cells, however, are affected by two-hit events, which can have an immediate effect.

The probability that a cell dies after experiencing single-hit event is a_{u_k} if the cell is active, and a_{q_k} if the cell is quiescent. Since only the active cells sustain two-hit event damage, we define the probability that a cell dies after experiencing a two-hit event as b_{u_k}. Therefore, the active cell compartment satisfies $b_{u_k} = O(1)$. Both cell types are equally susceptible to single-hit events, and so we assume $a_{u_k}, a_{q_k} = O(1)$.

For the active cells, we denote the numbers of single-hit and two-hit active sites h_i and g_i respectively. For the quiescent cells, the associated number of single-hit active sites is H_i. Since a two-hit event occurrence is negligible for the quiescent cells, we ignore two-hit active sites for these cells.

Recall that hit events are stochastically independent, and that two single-hit events close enough in time and space comprise a two-hit event. Then the probability that an active cell u_k dies is

$$\begin{aligned}\text{Prob}\,(u_k \text{ dies}) &= a_{u_k}\,\text{Prob}\,(u_k \text{ has at least one single-hit event}) \\ &\quad + b_{u_k}\,\text{Prob}\,(u_k \text{ has at least one two-hit event}) \\ &\quad - \max(a_{u_k}, b_{u_k})\,\text{Prob}\,(u_k \text{ has at least one single-hit event and one two-hit event}).\end{aligned}$$

The probability that a quiescent cell q_k dies is

$$\text{Prob}\,(q_k \text{ dies}) = a_{q_k}\,\text{Prob}\,(q_k \text{ has at least one single-hit event}).$$

Using expressions (4.1) and (4.2) we get that

$$\begin{aligned}\text{Prob}\,(u_k \text{ dies}) &= a_{u_k}\left(1-\prod_{i=1}^{h_i}(1-P_{H,i})\right)+b_{u_k}\left(1-\prod_{i=1}^{g_i}(1-P_{2H,i})\right) \\ &\quad -\max(a_{u_k},b_{u_k})\left(1-\prod_{i=1}^{h_i}(1-P_{H,i})\right)\left(1-\prod_{i=1}^{g_i}(1-P_{2H,i})\right)\end{aligned} \tag{4.3}$$

and

$$\text{Prob}\,(q_k \text{ dies}) = a_{q_k}\left(1-\prod_{i=1}^{H_i}(1-P_{H,i})\right). \tag{4.4}$$

In order to simplify the above probabilities, we make the assumption that all active cells are identical, and all quiescent cells are identical. This means that we have $a_{u_k}=a_u$, $a_{q_k}=a_q$, $b_{u_k}=b$, $h_i=h$, $g_i=g$, and $H_i=H$.

As a result of this assumption, probabilities (4.3) and (4.4) reduce respectively to

$$\begin{aligned}\text{Prob}\,(u_k \text{ dies}) &= a_u\left(1-(1-P_{H,i})^h\right)+b\left(1-(1-P_{2H,i})^g\right) \\ &\quad -\max(a_u,b)\left(1-(1-P_{H,i})^h\right)\left(1-(1-P_{2H,i})^g\right)\end{aligned} \tag{4.5}$$

and

$$\text{Prob}\,(q_k \text{ dies}) = a_q\left(1-(1-P_{H,i})^H\right) \tag{4.6}$$

where u_k and q_k now represent any active or quiescent cell.

Step 3: Radiation Physics

In this step, we derive expressions for the single-hit and two-hit event probabilities previously defined as $P_{H,i}$ and $P_{2H,i}$.

The probability that an active site d_i is hit by radiation in the time interval Δt is proportional to the energy imparted, as well the time interval. We let $D(t)$ denote the dose accumulated at time t, and so $R(t)=\frac{dD}{dt}$ is the radiation dose rate. We note that the inclusion of spatial cell distributions could be important as radiation can be scattered and altered. However, we assume that the energy imparted is homogeneous to leading order. We then have that

$$\begin{aligned}P_{H,i} &= \bar{\delta}\Delta t E \\ &= \delta\Delta t R(t).\end{aligned} \tag{4.7}$$

where $\delta R(t)$ becomes the probability density function of $P_{H,i}$.

In order to compute $P_{2H,i}$, we need to calculate the probability that two stochastically independent one-hit events occur close in time and space. We require that two single-hits occur in a time interval of length ω in order to produce a two-hit event.

Suppose that a single-hit event occurred in the time interval $[t - \Delta t, t]$. In order to have a two-hit event at time t, another single-hit must have occurred in the interval $[t - \omega, t]$. From above, we know that probability density of a single-hit event is $\delta R(t)$. So we define

$$\begin{aligned} F(\omega) &= \text{Prob (a single-hit event in } [t-\omega, t]) \\ &= \int_{t-\omega}^{t} \delta R(t) dt. \end{aligned}$$

Expand $F(\omega)$ about $\omega = 0$, using that $F(0) = 0$ and $F'(0) = \delta R(t)$.

$$\begin{aligned} F(\omega) &= \int_{t-\omega}^{t} \delta R(t) dt \\ &\approx F(0) + F'(0)\omega + O(\omega^2) \\ &= \delta R(t)\omega + O(\omega^2) \end{aligned}$$

Using this first order approximation for $F(\omega)$, we can now compute $P_{2H,i}$.

$$\begin{aligned} P_{2H,i} &= P_{H,i} F(\omega) \\ &= \delta R(t) \Delta t \delta R(t) \omega \\ &= \omega \delta^2 (R(t))^2 \Delta t \end{aligned}$$

We substitute these results into (4.5) and (4.6). These expressions are now functions of Δt, so we redefine them accordingly. The probability that an active cell dies as a result of radiation delivered over a time unit Δt is defined as $\Psi(\Delta t)$, and the probability that a quiescent cell dies as a result of radiation delivered over Δt is $\Phi(\Delta t)$. We have that

$$\begin{aligned} \Psi(\Delta t) &:= \text{Prob}\,(u_k \text{ dies}) \\ &= a_u \left(1 - (1 - \delta \Delta t R(t))^h\right) + b \left(1 - (1 - \omega \delta^2 R^2(t) \Delta t)^g\right) \\ &\quad - \max(a_u, b) \left(1 - (1 - \delta \Delta t R(t))^h\right) \left(1 - (1 - \omega \delta^2 R^2(t) \Delta t)^g\right) \end{aligned}$$

and

$$\begin{aligned}\Phi(\Delta t) &:= \text{Prob}\,(q_k \text{ dies}) \\ &= a_q\left(1-(1-\delta\Delta t R(t))^H\right).\end{aligned}$$

Step 4: Radiation Induced Death Rates

If $P(\text{death})$ denotes the probability of death in a time unit Δt, then

$$\Gamma := \lim_{\Delta t\to 0}\frac{P(\text{death})}{\Delta t}$$

defines the death rate. In order to find the death rates for both the active and the quiescent cells, we expand $\Psi(\Delta t)$ and $\Phi(\Delta t)$ about $\Delta t = 0$.

$$\begin{aligned}\Psi(\Delta t) &= \Psi(0)+\Psi'(0)\Delta t + O(\Delta t^2) \\ &= (a_u h\delta R(t) + bg\delta^2\omega R^2(t))\Delta t + O(\Delta t^2)\end{aligned}$$

$$\begin{aligned}\Phi(\Delta t) &= \Phi(0)+\Phi'(0)\Delta t + O(\Delta t^2) \\ &= (a_q H\delta R(t))\Delta t + O(\Delta t^2)\end{aligned}$$

Then the death rates for active and quiescent cells can be computed.

$$\begin{aligned}\Gamma_u &= \lim_{\Delta t\to 0}(a_u h\delta R(t) + bg\delta^2\omega R^2(t))\Delta t + O(\Delta t^2) \\ &= a_u h\delta R(t) + bg\delta^2\omega R^2(t) \qquad (4.8)\end{aligned}$$

$$\begin{aligned}\Gamma_q &= \lim_{\Delta t\to 0}(a_q H\delta R(t))\Delta t + O(\Delta t^2) \\ &= a_q H\delta R(t) \qquad (4.9)\end{aligned}$$

We define $A_1 = a_u h\delta$, $A_2 = a_q H\delta$, and $B = bg\delta^2\omega$. Then we write (4.8) and (4.9) as follows:

$$\Gamma_u = A_1 R(t) + BR^2(t) \qquad (4.10)$$

$$\Gamma_q = A_2 R(t) \qquad (4.11)$$

Step 5: ODE model

In order to use the above radiation induced death rates $\Gamma_u(t)$ and $\Gamma_q(t)$ in an ODE model, we first consider a cell cycle model for active and quiescent cells without the effects of radiation. Let $u(t)$ denote the density of active cells and $q(t)$ denote the density of quiescent cells. Further, let $f(u)$ denote the reproduction of active cells, where we assume that the two daughter cells enter the quiescent compartment at birth. Moreover, $\gamma > 0$ denotes the rate at which a quiescent cell becomes active. Then a simple cell cycle model is given as (see Swierniak [26])

$$\begin{aligned} u_t &= -f(u) + \gamma q \\ q_t &= 2f(u) - \gamma q. \end{aligned} \tag{4.12}$$

Now we include the additional effect of radiation, which interferes only indirectly with reproduction.

$$\begin{aligned} u_t &= -f(u) + \gamma q - \Gamma_u(t)u \\ q_t &= 2f(u) - \gamma q - \Gamma_q(t)q, \end{aligned} \tag{4.13}$$

where $\Gamma_q(t)$ and $\Gamma_u(t)$ are the rates defined above in (4.8) and (4.9).

Chapter 5

Analysis of the Active-Quiescent Radiation Model

In this chapter, we perform both linear analysis and perturbation analysis on the model (4.12) derived in Chapter 4. We first analyze the case where the dose rate is constant, and then consider the case where the dose rate is time dependent.

5.1 A First Linear Model With Constant Dose Rate R

In this section, we perform linear analysis on the active-quiescent model given by (4.12), with a constant dose rate, $R(t) = R$. We assume that the reproduction rate is a linear function of u, so we let $f(u) = \mu u$, with $\mu > 0$. The model is then given by the following two ODEs:

$$\begin{aligned} u_t &= -\mu u + \gamma q - \Gamma_u u \\ q_t &= 2\mu u - \gamma q - \Gamma_q q \,. \end{aligned} \tag{5.1}$$

We write (5.1) in matrix form

$$\begin{pmatrix} u \\ q \end{pmatrix}_t = \begin{pmatrix} -\mu - \Gamma_u & \gamma \\ 2\mu & -\gamma - \Gamma_q \end{pmatrix} \begin{pmatrix} u \\ q \end{pmatrix} \tag{5.2}$$

where we refer to the 2 x 2 matrix as J. This system has a unique equilibrium point $(0, 0)$, for all values of $R \neq R^*$, where R^* is a critical value of R, which gives a line of equilibria.

For future reference, we note that the trace and determinant of J are given by

$$\begin{aligned} \text{tr}J &= -\mu - \gamma - \Gamma_u - \Gamma_q \qquad (5.3) \\ \text{and} & \\ \det J &= -\mu\gamma + \mu\Gamma_q + \gamma\Gamma_u + \Gamma_u\Gamma_q. \qquad (5.4) \end{aligned}$$

We divide our analysis into four cases determined by the magnitude of the dose rate R, beginning with the instance where there is no radiation.

5.1.1 No Radiation : R = 0

In this case, either the treatment has not yet begun, which means that the accumulated dose is zero, $D = 0$, or the treatment has stopped, which corresponds with a constant accumulated dose, $D = constant$. Both cases imply that the dose rate is zero, and that $\Gamma_u = \Gamma_q = 0$. The trace and the determinant of equation (5.2) are

$$\text{tr}J = -\mu - \gamma < 0 \qquad \text{and} \qquad \det J = -\mu\gamma < 0\,,$$

and hence the unique equilibrium point $(0, 0)$ is a saddle point.

If $u \geq 0$ and $q \geq 0$ then $(u+q)_t = \mu u \geq 0$. Hence the positive quadrant is invariant and positive solutions are increasing in $u + q$.

The eigenvalues of J are

$$\lambda_{1,2} = -\frac{\mu+\gamma}{2} \pm \frac{1}{2}\sqrt{(\mu+\gamma)^2 + 4\mu\gamma} \quad ,$$

and satisfy $\lambda_1 > 0$ and $\lambda_2 < 0$. The corresponding eigenvectors are

$$Z_1 = \begin{pmatrix} \gamma \\ \lambda_1 + \mu \end{pmatrix}, \quad \text{and} \quad Z_2 = \begin{pmatrix} \gamma \\ \lambda_2 + \mu \end{pmatrix}.$$

Both components of Z_1 are positive, so the unstable manifold lies in the first and third quadrants. The second component of Z_2 satisfies

$$\begin{aligned} \lambda_2 + \mu &= -\frac{(\mu+\gamma)}{2} - \frac{1}{2}\sqrt{(\mu+\gamma)^2 - 4\gamma\mu} + \mu \\ &< -\frac{(\mu+\gamma)}{2} + \mu - \frac{(\mu+\gamma)}{2} \\ &= -\mu + \mu - \gamma \\ &= -\gamma \\ &< 0, \end{aligned}$$

so the stable manifold lies in the second and fourth quadrants. This confirms that solutions in the first quadrant are increasing in both u and q, and that the first quadrant is invariant.

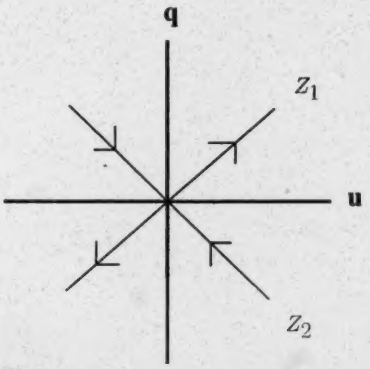

Figure 5.1: Schematic of the saddle point $(0,0)$. The unstable manifold enters the first and third quadrant and the stable manifold lies in the second and fourth quadrant.

Biologically, this means that in the case where there is no radiation administered, the number of both active and resting tumour cells will increase with time.

5.1.2 Dose Rate Small

Here, the dose rate R satisfies the condition

$$R^2(\gamma B + A_1A_2 + A_2B) + R(\mu A_2 + \gamma A_1) < \mu\gamma$$

so that $\det J < 0$.

This means we have eigenvalues with opposite signs, $\lambda_1 > 0$ and $\lambda_2 < 0$, and the unique equilibrium point $(0,0)$ is a saddle point.

The eigenvalues in this case are

$$\lambda_{1,2} = \frac{-\mu - \gamma - \Gamma_u - \Gamma_q}{2} \pm \frac{1}{2}\sqrt{(-\mu - \gamma - \Gamma_u - \Gamma_q)^2 - 4\det J},$$

with corresponding eigenvectors

$$Z_1 = \begin{pmatrix} \gamma \\ \lambda_1 + \mu + \Gamma_u \end{pmatrix} \quad \text{and} \quad Z_2 = \begin{pmatrix} \gamma \\ \lambda_2 + \mu + \Gamma_u \end{pmatrix}.$$

Since $\gamma > 0$ and $\lambda_1 + \mu + \Gamma_u > 0$, both components of Z_1 are positive, so the unstable manifold points in the positive direction. Also, since $\lambda_1 > 0$, we have that

$$\frac{-\mu-\gamma-K_1-K_2}{2} > \frac{1}{2}\sqrt{(-\mu-\gamma-K_1-K_2)^2-4\text{det}J},$$

which implies

$$\begin{aligned}
\lambda_2+\mu+K_1 &= -\frac{\mu+\gamma+K_1+K_2}{2} - \frac{1}{2}\sqrt{(-\mu-\gamma-K_1-K_2)^2-4\text{det}J} \\
&\quad +\mu+K_1 \\
&< -\frac{\mu+\gamma+K_1+K_2}{2} + \mu + K_1 - \frac{\mu+\gamma+K_1+K_2}{2} \\
&= -\mu-\gamma-K_1-K_2+\mu+K_1 \\
&= -\gamma-K_2 \\
&< 0.
\end{aligned}$$

So the second component of Z_2 is negative, which means that the stable manifold can never lie in the positive quadrant (see Figure 5.1).

This case is similar to the case with no radiation. The dose rate is so small that the treatment is ineffective, so the number of both active and resting cells continue to grow with time.

5.1.3 Critical Dose Rate

In this case, the dose rate satisfies $R^2(\gamma B + A_1A_2 + A_2B) + R(\mu A_2 + \gamma A_1) = \mu\gamma$ which implies $\det J = 0$. The eigenvalues are given by

$$\begin{aligned}
\lambda_1 &= \text{tr}J = -\mu-\gamma-\Gamma_u-\Gamma_q \\
\lambda_2 &= 0
\end{aligned}$$

with corresponding eigenvectors

$$Z_1 = \begin{pmatrix} -\gamma \\ \gamma+\Gamma_q \end{pmatrix} \quad \text{and} \quad Z_2 = \begin{pmatrix} \gamma \\ \mu+\Gamma_u \end{pmatrix}.$$

The general solution of the system (5.2) in this case is given by

$$\begin{pmatrix} u \\ q \end{pmatrix}(t) = C_1 e^{\text{tr}J\cdot t}\begin{bmatrix} -\gamma \\ \gamma+\Gamma_q \end{bmatrix} + C_2\begin{bmatrix} \gamma \\ \mu+\Gamma_u \end{bmatrix}$$

where $C_1 = \frac{1}{\mu+\gamma+\Gamma_u+\Gamma_q}\left[q(0) - \frac{u(0)(\mu+\Gamma_u)}{\gamma}\right]$ and $C_2 = \frac{1}{\mu+\gamma+\Gamma_u+\Gamma_q}\left[q(0) + \frac{u(0)(\gamma+\Gamma_q)}{\gamma}\right]$

The system no longer has a unique equilibrium, but a line of equilibria satisfying $u = \frac{\gamma}{\mu+\Gamma_u}q$ (see Figure 5.2). In this case, the number of tumour cells approaches a steady-state, which means the treatment is effective only in maintaining a constant tumour size.

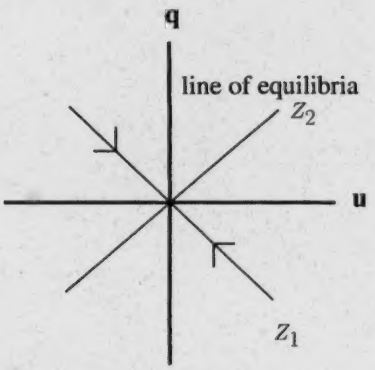

Figure 5.2: Schematic of the line of equilibria in the case of critical R.

5.1.4 Dose Rate Large

In this case we assume that the dose rate R satisfies $R^2(\gamma B + A_1A_2 + A_2B) + R(\mu A_2 + \gamma A_1) > \mu\gamma$, which implies that $\det J > 0$. We wish to rule out the case where $(0,0)$ is a stable spiral, since this is biologically unrealistic.

To have a stable spiral, we must have $(\mathrm{tr}J)^2 < 4 \cdot \det J$ and $\mathrm{tr}J < 0$. Using (5.3) and (5.4), we have that

$$\begin{aligned}(\mathrm{tr}J)^2 &= \mu^2 + \gamma^2 + \Gamma_u^2 + \Gamma_q^2 + 2\mu\gamma + 2\mu\Gamma_u + 2\gamma\Gamma_u + 2\mu\Gamma_q + 2\gamma\Gamma_q + 2\Gamma_u\Gamma_q \\ &< -4\mu\gamma + 4\mu\Gamma_q + 4\gamma\Gamma_u + 4\Gamma_u\Gamma_q\end{aligned}$$

Rearranging terms, we obtain the following requirement:

$$(\mu - \gamma + \Gamma_u - \Gamma_q)^2 < -8\mu\gamma.$$

This is impossible, due to the constraints on the parameters, so we can never have a stable spiral. Therefore, the unique equilibrium point (0,0) is a stable node (see Figure 5.3).

In this case, the treatment causes the number of both active and resting tumour cells to decrease to zero with time.

5.2 Singular Perturbation Analysis of the Cell Cycle Model without Radiation

The cell cycle and the quiescent phase critically depends on the values of μ and γ. For this reason, we study the effects of these two parameters on our active-quiescent

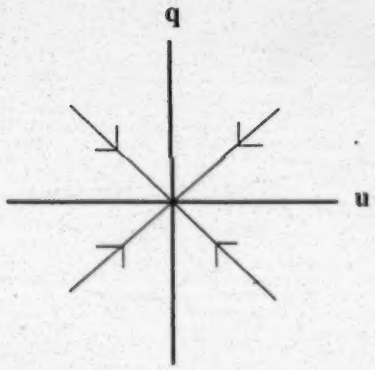

Figure 5.3: Schematic of the stable node $(0,0)$.

model. To do this, we use perturbation arguments. First we look at the case where there is no radiation. After this case is understood, we analyze the case where the model includes the effect of a time dependent death rate due to radiation.

In order to study the effects of the parameters γ and μ separately, we need a transformation that separates the actions of these two parameters.

5.2.1 A Useful Transformation

The cell cycle model without radiation, presented earlier, in (4.12), is

$$\begin{aligned} u_t &= -\mu u + \gamma q \\ q_t &= 2\mu u - \gamma q. \end{aligned} \tag{5.5}$$

We define new variables,

$$\begin{aligned} Z &= u + q \\ W &= 2u + q, \end{aligned} \tag{5.6}$$

where Z is equal to the total number of cells, and W is equal to newborn cells plus the number of resting cells.

We make the necessary substitutions to obtain a system in Z and W. This new system is given by the following ODEs,

$$\begin{aligned} Z_t &= \mu(W - Z) \\ W_t &= \gamma(2Z - W), \end{aligned} \tag{5.7}$$

and is equivalent to (5.5). This transformation successfully separated the actions of the parameters, μ and γ, so we use system (5.7) for our analysis.

5.2.2 The Case of γ Large and $\mu = O(1)$

The first case we consider is when the transition rate from the quiescent to the active cell compartment is large relative to the reproductive rate. We write $\gamma = \frac{\tilde{\gamma}}{\epsilon}$, and the model becomes

$$\begin{aligned} Z_t &= \mu(W - Z) \\ \epsilon W_t &= \tilde{\gamma}(2Z - W). \end{aligned} \tag{5.8}$$

We rescale time so that $\vartheta = \frac{t}{\epsilon}$, yielding

$$\begin{aligned} Z_\vartheta &= \epsilon\mu(W - Z) \\ W_\vartheta &= \tilde{\gamma}(2Z - W). \end{aligned} \tag{5.9}$$

Here ϑ is a fast time scale which describes the initial layer, while t is the slow time scale for the long-time behaviour [15]. We expand the variables in the fast system (5.9) as follows:

$$\begin{aligned} Z &= \hat{Z}_0 + \epsilon\hat{Z}_1 + \epsilon^2\hat{Z}_2 \ldots \\ W &= \hat{W}_0 + \epsilon\hat{W}_1 + \epsilon^2\hat{W}_2 \ldots . \end{aligned}$$

After substitution, we look at the leading order terms to obtain $\hat{Z_0}_\vartheta = 0 \Rightarrow \hat{Z}_0 = constant = \hat{Z}_0(0)$, and

$$\begin{aligned} \hat{W_0}_\vartheta &= \tilde{\gamma}(2\hat{Z}_0(0) - \hat{W}_0) \\ \Rightarrow \hat{W}_0(\vartheta) &= (\hat{W}_0(0) - 2\hat{Z}_0(0))e^{-\tilde{\gamma}\vartheta} + 2\hat{Z}_0(0) \end{aligned}$$

which converges to $2\hat{Z}_0(0)$ for $\vartheta \to \infty$.

To match the fast and slow systems together, we let $\vartheta \to \infty$ for the fast system solutions, and take these limits as initial conditions for the slow system. The initial conditions for the slow system are: $z_0(t = 0) = \hat{Z}_0(0)$ and $w_0(t = 0) = 2\hat{Z}_0(0)$.

We expand the variables of the slow system (5.8),

$$\begin{aligned} Z &= z_0 + \epsilon z_1 + \epsilon^2 z_2 \ldots \\ W &= w_0 + \epsilon w_1 + \epsilon^2 w_2 \ldots \end{aligned}$$

and after substitution we take the leading-order terms which give

$$z_{0t} = \mu(w_0 - z_0) \tag{5.10}$$
$$0 = \tilde{\gamma}(2z_0 - w_0). \tag{5.11}$$

From (5.11) we have that $w_0 = 2z_0$, so equation (5.10) reduces to $z_{0t} = \mu z_0$. Solving this with the specified initial condition gives

$$z_0(t) = \hat{Z}_0(0)e^{\mu t}.$$

This implies that

$$w_0(t) = 2\hat{Z}_0(0)e^{\mu t}.$$

For a fast transition rate from the resting to active cell compartment, we find that the total number of tumour cells grows exponentially with rate μ.

5.2.3 The Case of μ Large and $\gamma = O(1)$

In this case, we assume that the reproductive rate is large relative to the transition rate from quiescent to active compartment. We write $\mu = \frac{\tilde{\mu}}{\epsilon}$.

The slow system is given by

$$\epsilon Z_t = \tilde{\mu}(W - Z), \tag{5.12}$$
$$W_t = \gamma(2Z - W), \tag{5.13}$$

whereas the fast system is

$$Z_\vartheta = \tilde{\mu}(W - Z), \tag{5.14}$$
$$W_\vartheta = \epsilon\gamma(2Z - W). \tag{5.15}$$

Using the same process as the previous case, from (5.15), we have

$$\hat{W}_{0\vartheta} = 0,$$

which implies that

$$\hat{W}_0(\vartheta) = \hat{W}_0(0).$$

From (5.14) we have

$$\hat{Z}_{0\vartheta} = \tilde{\mu}(\hat{W}_0(0) - \hat{Z}_0),$$

and solving this for $\hat{Z}_0(\vartheta)$ we get

$$\hat{Z}_0(\vartheta) = e^{-\tilde{\mu}t}(\hat{Z}_0 - \hat{W}_0(0)) + \hat{W}_0(0). \tag{5.16}$$

For $\vartheta \to \infty$, (5.16) converges to $\hat{W}_0(0)$.

As in the previous case of (5.2.2), we match the fast and slow systems together by taking $\vartheta \to \infty$ in the fast system solutions and take these limits as initial conditions for the slow system. The initial conditions for the slow system are: $z_0(t=0) = \hat{Z}_0(0)$ and $w_0(t=0) = \hat{W}_0(0)$.

From equation (5.12) in the slow system, we have

$$0 = \tilde{\mu}(w_0 - z_0),$$

which implies that $z_0 = w_0$. From (5.13), the second equation in the fast system, we replace w_0 with z_0 to get

$$\begin{aligned} Z_{0t} &= \gamma(2Z_0 - Z_0) \\ &= \gamma Z_0, \end{aligned}$$

with solution $Z_0 = Z_0(0)e^{\gamma t}$.

For reproductive rate large, and transition rate small, the total number of cells grows exponentially with rate γ.

5.3 Singular Perturbation Analysis for a Time Dependent Dose Rate

In this section, we study a dose rate $R(t)$ which varies with time, and investigate the effects of the parameters μ and γ on the system 5.1.

Again, the cell cycle model is given by the following two ODEs:

$$\begin{aligned} u_t &= -\mu u + \gamma q - \Gamma_u(t)u \\ q_t &= 2\mu u - \gamma q - \Gamma_q(t)q. \end{aligned} \tag{5.17}$$

5.3.1 Slow Transition Between Active and Quiescent Compartments, and Slow Proliferation

The first case we look at is when both γ and μ are small. We let

$$\tilde{\gamma} = \epsilon\gamma \quad , \quad \tilde{\mu} = \epsilon\mu$$

where ϵ is small. Substituting these values into the active-quiescent model (5.17) yields

$$\begin{aligned} u_t &= -\epsilon\tilde{\mu}u + \epsilon\tilde{\gamma}q - \Gamma_u(t)u \\ q_t &= 2\epsilon\tilde{\mu}u - \epsilon\tilde{\gamma}q - \Gamma_q(t)q. \end{aligned}$$

Now expand both u and q as follows:

$$\begin{aligned} u &= u_0 + \epsilon u_1 + \epsilon^2 u_2 + \dots \\ q &= q_0 + \epsilon q_1 + \epsilon^2 q_2 + \dots . \end{aligned}$$

Substitute these expansions into the model, and take the leading-order terms to get the system

$$\begin{aligned} u_{0t} &= -\Gamma_u(t)u_0 \\ q_{0t} &= -\Gamma_q(t)q_0. \end{aligned}$$

Solving this system gives

$$\begin{aligned} u_0(t) + q_0(t) &= u_0(0)e^{-\int_0^t \Gamma_u dt} + q_0(0)e^{-\int_0^t \Gamma_q dt} \qquad (5.18) \\ &= u_0(0)e^{-A_1 D(t) - B\int_0^t R^2(t)dt} + q_0(0)e^{-A_2 D(t)} \\ \|u_0(t) + q_0(t)\| &\leq C_1 e^{-A_1 D(t) - B\int_0^t R^2(t)dt} + C_2 e^{-A_2 D(t)}. \qquad (5.19) \end{aligned}$$

The case of $R(t) = R = constant$ reduces to:

$$\begin{aligned} u_0(t) + q_0(t) &= u_0(0)e^{-\Gamma_u t} + q_0(0)e^{-\Gamma_q t} \\ \|u_0(t) + q_0(t)\| &\leq C_1 e^{-A_1 Rt - BR^2 t} + C_2 e^{-A_2 Rt}. \qquad (5.20) \end{aligned}$$

We note that equation (5.20) is a modified linear quadratic model, where the difference is the addition of the term that accounts for quiescent cell damage due to one-hit events.

5.3.2 Transformation With Radiation

Now we apply the transformation (5.6) to the cell cycle model with radiation presented in (5.1). First we calculate the equation for $Z = u + q$

$$\begin{aligned} Z_t &= \mu N - \Gamma_u N - \Gamma_q R \\ &= (\mu - \Gamma_u)(W - Z) - \Gamma_q(2Z - W) \\ &= (-\mu + \Gamma_u - 2\Gamma_q)Z + (\mu - \Gamma_u + \Gamma_q)W. \end{aligned}$$

We also calculate the equation for $W = 2u + q$:

$$\begin{aligned} W_t &= \gamma R - 2\Gamma_u N - \Gamma_q R \\ &= \gamma(2Z - W) - \Gamma_q(2Z - W) - 2\Gamma_u(W - Z) \\ &= (2\gamma + 2\Gamma_u - 2\Gamma_q)Z + (\Gamma_q - \gamma - 2\Gamma_u)W. \end{aligned}$$

The transformed system is:

$$\begin{aligned} Z_t &= (\Gamma_u(t) - 2\Gamma_q(t) - \mu)Z + (\mu - \Gamma_u(t) + \Gamma_q(t))W \\ W_t &= (2\Gamma_u(t) - 2\Gamma_q(t) + 2\gamma)Z + (\Gamma_q(t) - \gamma - 2\Gamma_u(t))W. \end{aligned} \tag{5.21}$$

5.3.3 The Case of γ Large and $\mu = O(1)$

Here we again consider the case where the transition rate from the quiescent to the active cell compartment is large compared to the proliferation rate. We write $\gamma = \frac{\tilde{\gamma}}{\epsilon}$, and the system (5.21) becomes

$$Z_t = (\Gamma_u - 2\Gamma_q - \mu)Z + (\mu - \Gamma_u + \Gamma_q)W \tag{5.22}$$

$$\epsilon W_t = (2\tilde{\gamma} - 2\epsilon\Gamma_q + 2\epsilon\Gamma_u)Z + (\epsilon\Gamma_q - \tilde{\gamma} - 2\epsilon\Gamma_u)W. \tag{5.23}$$

We take the leading order terms of (5.23),

$$2\tilde{\gamma}Z_0 + (-\tilde{\gamma}W_0) = 0$$

and rearranging we get $W_0 = 2Z_0$. We substitute this result into (5.22) to get

$$\begin{aligned} Z_{0t} &= (\Gamma_u - 2\Gamma_q - \mu)Z_0 + (\mu - \Gamma_u + \Gamma_q)2Z_0 \\ &= (\mu - \Gamma_u)Z_0 \end{aligned} \tag{5.24}$$

which can be solved to obtain

$$Z_0(t) = Z_0(0)e^{(\mu t - A_1 D(t) - \int_0^t BR^2 dt)}. \tag{5.25}$$

In the special case where $R(t) = R = constant$, the solution to (5.24) is

$$Z_0(t) = Z_0(0)e^{(\mu - A_1 R - BR^2)\cdot t}.$$

If μ is small, we obtain a dose rate dependent linear quadratic model with $\alpha = A_1 t$ and $\beta = Bt$. Notice that the one hit event damage on the resting cells, A_2 has

no effect in this case. This means that the active cells control the system dynamics when the transition rate γ is large. This agrees with the biological behaviour, since new cells would spend much less time in the quiescent compartment before entering the active phase of the cell cycle.

5.3.4 The Case of μ Large and $\gamma = O(1)$

Here we consider that the proliferation rate is large relative to the transition rate. We write $\mu = \frac{\tilde{\mu}}{\epsilon}$, and then system (5.21) becomes

$$\epsilon Z_t = (\epsilon\Gamma_u - 2\epsilon\Gamma_q - \tilde{\mu})Z + (\tilde{\mu} - \epsilon\Gamma_u + \epsilon\Gamma_q)W \quad (5.26)$$

$$W_t = (2\gamma - 2\Gamma_q + 2\Gamma_u)Z + (\Gamma_q - \gamma - 2\Gamma_u)W. \quad (5.27)$$

We take the leading order terms of (5.26) to obtain

$$0 = -\tilde{\mu}Z_0 + \tilde{\mu}W_0$$

which implies that $W_0 = Z_0$. Use this result to simplify (5.27), and it is then given by

$$\begin{aligned} Z_{0t} &= (2\gamma - 2\Gamma_q + 2\Gamma_u)Z_0 + (\Gamma_q - \gamma - 2\Gamma_u)Z_0 \\ &= (\gamma - \Gamma_q)Z_0. \end{aligned} \quad (5.28)$$

We solve (5.28) to get

$$Z_0(t) = Z_0(0)e^{\gamma t - A_2 D(t)}. \quad (5.29)$$

In the special case where $R(t) = R$, the solution to (5.28) is given by

$$Z_0(t) = Z_0(0)e^{(\gamma - A_2 R)t}. \quad (5.30)$$

In this case, where the transition from quiescent to active is slow relative to proliferation, the A_2R-term dominates, while the effect of the radiation on the active cells does not contribute to the first order system behaviour. Again, this makes sense because new cells quickly accumulate in the quiescent compartment, and therefore, although less sensitive to radiation, the higher density of cells found here causes this compartment to control the system dynamics.

5.3.5 The Case of μ Large and γ Large

The case where both μ and γ are large corresponds to a fast reproduction rate and a fast transition rate from the resting to the active cell compartment. Perturbation arguments show that this case reduces to the instance where the death due to radiation is negligible, and therefore provides no further insight to the system behaviour.

5.3.6 Model Comparison

We investigate the relationship between the parameters in the active-quiescent model, μ and γ, with the parameters in the LQ Model, α and β, for the case where R is constant. Typically, a small α/β ratio corresponds with a slow cell cycle, whereas a larger parameter ratio indicates a fast cell cycle. We summarize our findings in Table 5.1 below.

Case	μ	γ	α	β
1	small	small	$\min(A_1, A_2)$	B
2	large	small	A_2	0
3	small	large	A_1	B

Table 5.1: Comparison between the parameters in the active-quiescent model, μ and γ, and the parameters in the LQ Model, α and β, for the case where R is constant.

Case 1

In this case, we have that both μ and γ are small, which corresponds with a slow cell cycle and a significant quiescent phase. We found that our α/β ratio is equal to $min(A_1, A_2)/B$. In the classical interpretation, a slow cell cycle corresponds with a small α/β ratio. Our ratio is relatively small, which confirms this classical interpretation.

Case 2

In this case, we have that μ is large and γ is small, which corresponds with a fast cell cycle. We obtained the ratio $\alpha/\beta \to \infty$, which confirms the classical interpretation, in which the ratio is assumed to be large.

Case 3

In this third case, we have that μ is small, and γ is large. This corresponds with slow reproduction and effectively no quiescent compartment. We find that our α/β ratio in this case is A_1/B. In the classical interpretation, the α/β ratio should be

relatively small.

From this comparison, we find that a large α/β ratio indicates the presence of a significant quiescent compartment.

Chapter 6

Birth-Death Processes

In this section, we derive an expression for the tumour control probability (TCP) of system (4.13). The TCP is the probability that no malignant cells are left in an affected region. This is a useful tool in predetermining the success of radiotherapy treatment over time for a cancer patient.

In order to derive the TCP, we first describe the biological process using a birth-death process. This birth-death process is described by a system of infinitely many differential equations, which we solve using generating functions. The solutions obtained from this system form the components of the TCP. Once derived, the TCP determines the success of different treatment strategies.

6.1 The Corresponding Birth-Death Process

A birth-death process is a homogenous, aperiodic, irreducible markov chain with a discrete state space, where state transitions can occur only between neighbouring states. In our case, the state space of the birth-death process is the number of active and quiescent cells, respectively. Also, in our case, the birth-death process will be a continuous-time process.

We begin by defining $P_i(t)$ as the probability that i active cells are alive at time t, and similarly, $Q_j(t)$ as the probability that j resting cells are alive at time t. If $i, j < 0$, then we define $P_i(t)$ and $Q_j(t)$ to be equal to zero. Also, at time equal to zero, the density of active cells is defined to be $u(0)$, which implies that $P_{u(0)}(0) = 1$. At time zero, the density of resting cells is defined as $q(0)$, which implies that $Q_{q(0)}(0) = 1$. We are interested in finding the probability that no malignant cells are left in the affected region, i.e. the TCP. In particular, $\text{TCP}(t) = P_0(t)Q_0(t)$.

In order to determine equations for both $P_i(t)$ and $Q_j(t)$, we must recall the biological process we intend to describe. First we consider a single active cell. This cell must have entered the active compartment from the resting cell compartment. Once a cell becomes active, it can: leave the active cell compartment by replicating;

undergo cell death due to radiation; or it can remain in the active cell compartment.

Next we consider a single quiescent cell. This cell must have entered the quiescent compartment from the active compartment. It is important to note, however, that when a cell leaves the active compartment, it replicates, and two cells must enter the quiescent compartment. This implies that it is never the case that the number of resting cells increases by only one. Once a cell has become quiescent, it can: leave the quiescent cell compartment by becoming active; undergo cell death due to radiation; or it can remain in the quiescent cell compartment.

6.1.1 The Discrete Time BDP

In order to mathematically describe the birth-death process, we consider events that can occur in a very small time interval, $[t, t + \Delta t]$. One of the conditions of a birth-death process is that only one event can occur in this small time interval. Below we compute expression for both $P_i(t + \Delta t)$ and $Q_j(t + \Delta t)$.

Suppose we have i cells in the active compartment at time $t + \Delta t$. To write an expression for $P_i(t + \Delta t)$, we consider what could have happened in the time interval $[t, t + \Delta t]$. There are three possibilities and each possibility corresponds with a term in the resulting equation.

- If there were $i+1$ active cells at time t, then in the time interval considered, a single cell left the active cell compartment. Cells can leave by dying with rate Γ_u, or by replicating with rate μ. The probability of losing one of $i+1$ active cells in the time interval equals the product of: the probability of having $i+1$ active cells at time t; the number of cells at time t, which is $i + 1$; the sum of the rates at which a cells can leave the active compartment, $\Gamma_u + \mu$; and the length of the time interval, Δt. Mathematically, this is $(\mu + \Gamma_u)(i + 1)P_{i+1}(t)\Delta t$.

- If there were $i - 1$ active cells at time t, then a single cell entered the active cell compartment in the time interval $[t, t + \Delta t]$. The only way which cells can enter this compartment is directly from the resting cell compartment, with rate γ. The term that accounts for this case is different from the previous case in that instead of multiplying by the number of active cells, we must consider how many quiescent cells there were at time t. For this, we use the expected value of the density of resting cells at time t, $\sum_{j=1}^{\infty} jQ_j(t)$. The probability of gaining one active cell in $[t, t + \Delta t]$ is the product of: the expected value of the density of resting cells; the probability of having $i - 1$ active cells at time t; the rate at which quiescent cells become active, γ; and the length of the time interval, Δt. Mathematically, this is $\gamma \sum_{j=1}^{\infty} jQ_j(t)P_{i-1}(t)\Delta t$.

- If there were i active cells at time t, then no cells have left or entered the active cell compartment in the considered time interval. This is calculated by taking

$(P_i(t)$ − (Probability that a cell left the active compartment in $[t, t+\Delta t]$ + Probability that a cell entered the active compartment in $[t, t+\Delta t]$)). Using our results from the previous two cases, the associated expression is given by $\Big(1-\Delta t\big(\mu i+\Gamma_u i+\gamma\sum_{j=1}^{\infty} jQ_j(t)\big)\Big)P_i(t)$.

Now we take the sum of the terms associated with each of the above three cases, and obtain an equation for $P_i(t+\Delta t)$. For $i \geq 1$, we have

$$\begin{aligned} P_i(t+\Delta t) &= (\mu+\Gamma_u)(i+1)P_{i+1}(t)\Delta t+\gamma\sum_{j=1}^{\infty} jQ_j(t)P_{i-1}(t)\Delta t \\ &\quad +\Big(1-\Delta t\big(\mu i+\Gamma_u i+\gamma\sum_{j=1}^{\infty} jQ_j(t)\big)\Big)P_i(t). \end{aligned} \tag{6.1}$$

Here we suppose that we have j cells in the quiescent cell compartment at time $t+\Delta t$. In order to write an expression for $Q_j(t+\Delta t)$, we consider all events that could have occurred in time interval $[t, t+\Delta t]$.

- If there were $j+1$ quiescent cells at time t, a single cell left the resting cell compartment in the time interval considered. Cells can leave by dying with rate Γ_q, or by becoming active with rate γ. The associated term for this case is the product of: the probability of having $j+1$ resting cells at time t; the number of resting cells at time t, $j+1$; the sum of the rates at which cells can leave this compartment, $\Gamma_q+\gamma$; and the length of time interval, Δt. Mathematically this is $(\gamma+\Gamma_q)(j+1)Q_{j+1}(t)\Delta t$.

- If there were $j-2$ quiescent cells at time t, then two cells entered the quiescent cell compartment in the time interval $[t, t+\Delta t]$. Cells can become quiescent only after a cell replicates, at which point both daughter cells enter directly into this compartment with rate μ. The expression describing this case is the product of: the probability of having $j-2$ cells at time t; the expected value of the number of active cells at time t, $\sum_{i=1}^{\infty} iP_i(t)$; the rate at which cells become quiescent, μ; and the length of the time interval, Δt. Mathematically, this is $\mu\sum_{i=1}^{\infty} iP_i(t)Q_{j-2}(t)\Delta t$.

- If there were j cells at time t, then no cells left or entered the quiescent cell compartment in the time interval considered. The probability is calculated by taking $(Q_j(t)$ − (Probability that a cell left the resting compartment in $[t, t+\Delta t]$+ Probability that two cells entered the resting compartment in $[t, t+\Delta t]$)). Using information from the previous two cases, this expression is given by $\Big(1-\Delta t\big(\gamma j+\Gamma_q j+\mu\sum_{i=1}^{\infty} iP_i(t)\big)\Big)Q_j(t)$.

We take the sum of these three cases to obtain an expression for $Q_j(t+\Delta t)$. For $j \geq 0$, we have

$$\begin{aligned} Q_j(t+\Delta t) &= (\gamma+\Gamma_q)(j+1)Q_{j+1}(t)\Delta t + \mu\sum_{i=1}^{\infty} iP_i(t)Q_{j-2}(t)\Delta t \\ &\quad +\Big(1-\Delta t\big(\gamma j+\Gamma_q j+\mu\sum_{i=1}^{\infty} iP_i(t)\big)\Big)Q_j(t). \end{aligned} \tag{6.2}$$

6.1.2 The Continuous Time BDP

We would like to write these equations in differential form. Rearranging the terms in both (6.1) and (6.2), we obtain:

$$\begin{aligned} P_i(t+\Delta t)-P_i(t) &= (\mu+\Gamma_u)(i+1)P_{i+1}(t)\Delta t \\ &\quad +\gamma\sum_{j=1}^{\infty} jQ_j(t)P_{i-1}(t)\Delta t \\ &\quad -\Delta t\big(\mu i+\Gamma_u i+\gamma\sum_{j=1}^{\infty} jQ_j(t)\big)P_i(t) \end{aligned} \tag{6.3}$$

and

$$\begin{aligned} Q_j(t+\Delta t)-Q_j(t) &= (\gamma+\Gamma_q)(j+1)Q_{j+1}(t)\Delta t \\ &\quad +\mu\sum_{i=1}^{\infty} iP_i(t)Q_{j-2}(t)\Delta t \\ &\quad -\Delta t\big(\gamma j+\Gamma_q j+\mu\sum_{i=1}^{\infty} iP_i(t)\big)Q_j(t). \end{aligned} \tag{6.4}$$

Now we divide each side by Δt, and take the limit as Δt goes to zero of each side to obtain

$$\begin{aligned} \lim_{\Delta t\to 0}\frac{P_i(t+\Delta t)-P_i(t)}{\Delta t} &= \lim_{\Delta t\to 0}\Big[(\mu+\Gamma_u)(i+1)P_{i+1}(t) \\ &\quad +\gamma\sum_{j=1}^{\infty} jQ_j(t)P_{i-1}(t) \\ &\quad -\big(\mu i+\Gamma_u i+\gamma\sum_{j=1}^{\infty} jQ_j(t)\big)P_i(t)\Big] \end{aligned} \tag{6.5}$$

and

$$\lim_{\Delta t\to 0}\frac{Q_j(t+\Delta t)-Q_j(t)}{\Delta t} = \lim_{\Delta t\to 0}\Big[(\gamma+\Gamma_q)(j+1)Q_{j+1}(t) + \mu\sum_{i=1}^{\infty} iP_i(t)Q_{j-2}(t) - \big(\gamma j+\Gamma_q j+\mu\sum_{i=1}^{\infty} iP_i(t)\big)Q_j(t)\Big]. \tag{6.6}$$

On the left hand side of both (6.5) and (6.6), by the definition of the derivative, we have $\dot{P}_i(t)$ and $\dot{Q}_j(t)$ respectively. On the right hand sides of these equations, Δt does not appear, so taking the limit as Δt goes to zero leaves them unchanged.

We write equations (6.5) and (6.6) in differential form as follows:

$$\dot{P}_i(t) = (\mu+\Gamma_u)(i+1)P_{i+1}(t)+\gamma\sum_{j=1}^{\infty} jQ_j(t)P_{i-1}(t) - (\mu+\Gamma_u)iP_i(t)-\gamma\sum_{j=1}^{\infty} jQ_j(t)P_i(t) \tag{6.7}$$

and

$$\dot{Q}_j(t) = (\gamma+\Gamma_q)(j+1)Q_{j+1}(t)+\mu\sum_{i=1}^{\infty} iP_i(t)Q_{j-2}(t) - (\gamma+\Gamma_q)jQ_j(t)-\mu\sum_{i=1}^{\infty} iP_i(t)Q_j(t). \tag{6.8}$$

Equations (6.7) and (6.8) describe the birth-death process of the active-quiescent radiation model.

The expected values of $P_i(t)$ and $Q_j(t)$ are given by the respective densities of the active and quiescent cells, earlier defined as $u(t)$ and $q(t)$, so we have

$$u(t)=\sum_{i=1}^{\infty} iP_i(t) and q(t)=\sum_{j=1}^{\infty} jQ_j(t).$$

6.1.3 Mean Field Approximation of the Birth-Death Process

The birth-death process above describes the same biological process as the system (4.13), and in order to show they are equivalent, we derive (4.13) from the birth-death process (6.7) and (6.8).

We begin by multiplying equation (6.7) by i, and then take the sum from $i = 1$ to $i = \infty$ of both sides to obtain:

$$\begin{aligned}\sum_{i=1}^{\infty} i\dot{P}_i(t) &= (\mu+\Gamma_u)\sum_{i=1}^{\infty} i(i+1)P_{i+1}(t) \\ &\quad +\gamma\sum_{j=1}^{\infty} jQ_j(t)\sum_{i=1}^{\infty} iP_{i-1}(t) \\ &\quad -(\mu+\Gamma_u)\sum_{i=1}^{\infty} i^2P_i(t) - \gamma\sum_{j=1}^{\infty} jQ_j(t)\sum_{i=1}^{\infty} iP_i(t).\end{aligned} \tag{6.9}$$

We replace the expected values of $P_i(t)$ and $Q_j(t)$ with $u(t)$ and $q(t)$ where possible, and simplify to obtain:

$$\begin{aligned}\dot{u}(t) &= (\mu+\Gamma_u)\sum_{i=1}^{\infty}(i+1)^2P_{i+1}(t) - (\mu+\Gamma_u)\sum_{i=1}^{\infty}(i+1)P_{i+1}(t) \\ &\quad +\gamma q(t)\sum_{i=1}^{\infty}(i-1)P_{i-1}(t) + \gamma q(t)\sum_{i=1}^{\infty} P_{i-1}(t) \\ &\quad -(\mu+\Gamma_u)\sum_{i=1}^{\infty} i^2P_i(t) - \gamma q(t)u(t).\end{aligned} \tag{6.10}$$

Changing indices, using $n = i - 1$ in the third and fourth sums, and $m = i + 1$ in the first two sums, we obtain:

$$\begin{aligned}\dot{u}(t) &= (\mu+\Gamma_u)\sum_{m=2}^{\infty} m^2P_m(t) - (\mu+\Gamma_u)\sum_{m=2}^{\infty} mP_m(t) \\ &\quad +\gamma q(t)\sum_{n=0}^{\infty} nP_n(t) + \gamma q(t)\sum_{n=0}^{\infty} P_n(t) \\ &\quad -(\mu+\Gamma_u)\sum_{i=1}^{\infty} i^2P_i(t) - \gamma q(t)u(t).\end{aligned} \tag{6.11}$$

We use that $\sum_{n=0}^{\infty} P_n(t) = 1$ by definition, and add and subtract $(\mu + \Gamma_u)P_1(t)$ from the right hand side to obtain

$$\begin{aligned}\dot{u}(t) &= (\mu+\Gamma_u)\sum_{m=2}^{\infty} m^2 P_m(t) + (\mu+\Gamma_u)P_1(t) - (\mu+\Gamma_u)\sum_{m=2}^{\infty} mP_m(t) \\ &\quad -(\mu+\Gamma_u)P_1(t) + \gamma q(t)\sum_{n=0}^{\infty}(n)P_n(t) + \gamma q(t) \\ &\quad -(\mu+\Gamma_u)\sum_{i=1}^{\infty} i^2 P_i(t) - \gamma q(t)u(t).\end{aligned} \tag{6.12}$$

Again, adjust the indices, and substitute $u(t)$ and $q(t)$ where possible:

$$\begin{aligned}\dot{u}(t) &= (\mu+\Gamma_u)\sum_{m=1}^{\infty} m^2 P_m(t) - (\mu+\Gamma_u)\sum_{m=1}^{\infty} mP_m(t) \\ &\quad +\gamma q(t)u(t) + \gamma q(t) - (\mu+\Gamma_u)\sum_{i=1}^{\infty} i^2 P_i(t) - \gamma q(t)u(t).\end{aligned} \tag{6.13}$$

Simplify to obtain the first equation of (4.13)

$$\dot{u}(t) = -(\mu+\Gamma_u)u(t) + \gamma q(t).$$

We carry through similar steps for (6.8). Multiply by j, and then take the sum from $j=1$ to $j=\infty$ on both sides to obtain:

$$\begin{aligned}\sum_{j=1}^{\infty} j\dot{Q}_j(t) &= (\gamma+\Gamma_q)\sum_{j=1}^{\infty} j(j+1)Q_{j+1}(t) \\ &\quad +\mu\sum_{i=1}^{\infty} iP_i(t)\sum_{j=1}^{\infty} jQ_{j-2}(t) \\ &\quad -(\gamma+\Gamma_q)\sum_{j=1}^{\infty} j^2 Q_j(t) - \mu\sum_{i=1}^{\infty} iP_i(t)\sum_{j=1}^{\infty} jQ_j(t).\end{aligned} \tag{6.14}$$

We again replace the expected values of $P_i(t)$ and $Q_j(t)$ with $u(t)$ and $q(t)$ where possible, and simplify to obtain

$$\begin{aligned}\dot{q}(t) &= (\gamma+\Gamma_q)\sum_{j=1}^{\infty}(j+1)^2Q_{j+1}(t)\\ &\quad -(\gamma+\Gamma_q)\sum_{j=1}^{\infty}(j+1)Q_{j+1}(t)\\ &\quad +\mu u(t)\sum_{j=1}^{\infty}jQ_{j-2}(t)-(\gamma+\Gamma_q)\sum_{j=1}^{\infty}j^2Q_j(t)-\mu u(t)q(t).\end{aligned} \tag{6.15}$$

Adjust indices, using $m = j+1$ in the first two terms, and $n = j-2$ in the third term to obtain

$$\begin{aligned}\dot{q}(t) &= (\gamma+\Gamma_q)\sum_{m=2}^{\infty}(m)^2Q_m(t)-(\gamma+\Gamma_q)\sum_{m=2}^{\infty}(m)Q_m(t)\\ &\quad +\mu u(t)\sum_{n=0}^{\infty}(n+2)Q_n(t)-(\gamma+\Gamma_q)\sum_{j=1}^{\infty}j^2Q_j(t)-\mu u(t)q(t).\end{aligned} \tag{6.16}$$

We add and subtract $(\gamma+\Gamma_q)Q_1(t)$ from the right hand side, and simplify

$$\begin{aligned}\dot{q}(t) &= (\gamma+\Gamma_q)\sum_{m=2}^{\infty}(m)^2Q_m(t)+(\gamma+\Gamma_q)Q_1(t)-(\gamma+\Gamma_q)\sum_{m=2}^{\infty}(m)Q_m(t)\\ &\quad -(\gamma+\Gamma_q)Q_1(t)+\mu u(t)\sum_{n=0}^{\infty}nQ_n(t)\\ &\quad +2\mu u(t)\sum_{n=0}^{\infty}Q_n(t)-(\gamma+\Gamma_q)\sum_{j=1}^{\infty}j^2Q_j(t)-\mu u(t)q(t).\end{aligned} \tag{6.17}$$

Use that $\sum_{n=0}^{\infty}Q_n(t)=1$ by definition, and adjust indices to obtain:

$$\begin{aligned}\dot{q}(t) &= (\gamma+\Gamma_q)\sum_{m=1}^{\infty}(m)^2Q_m(t)+-(\gamma+\Gamma_q)\sum_{m=1}^{\infty}(m)Q_m(t)\\ &\quad +\mu u(t)q(t)+2\mu u(t)-(\gamma+\Gamma_q)\sum_{j=1}^{\infty}j^2Q_j(t)-\mu u(t)q(t).\end{aligned} \tag{6.18}$$

Finally, we simplify to obtain the second equation in system (4.13):

$$\dot{q}(t) = -(\gamma + \Gamma_q)q(t) + 2\mu u(t).$$

We have shown that the active-quiescent radiation model (4.13) derived earlier is the mean field approximation of the birth-death process described by (6.7) and (6.8).

6.1.4 Solution of the Birth-Death Process

We would like to solve the birth-death process, given by the system of infinitely many equations

$$\begin{aligned}\dot{P}_i(t) &= (\mu + \Gamma_u)(i+1)P_{i+1}(t) + \gamma q(t)P_{i-1}(t) \\ &\quad -(\mu + \Gamma_u)iP_i(t) - \gamma q(t)P_i(t)\end{aligned} \tag{6.19}$$

$$\begin{aligned}\dot{Q}_j(t) &= (\gamma + \Gamma_q)(j+1)Q_{j+1}(t) + \mu u(t)Q_{j-2}(t) \\ &\quad -(\gamma + \Gamma_q)jQ_j(t) - \mu u(t)Q_j(t).\end{aligned} \tag{6.20}$$

In order to solve the system of equations (6.19) and (6.20), we define generating functions $A(s,t)$ and $B(s,t)$ as follows:

$$A(s,t) = \sum_{i=0}^{\infty} P_i(t)s^i \tag{6.21}$$

$$B(s,t) = \sum_{j=0}^{\infty} Q_j(t)s^j. \tag{6.22}$$

We would like to determine the closed form equations for our system using these generating functions. We begin with $A(s,t)$. We have:

$$\frac{\partial A}{\partial t} = \sum_{i=0}^{\infty} \dot{P}_i(t)s^i. \tag{6.23}$$

We substitute the equation for $\dot{P}_i(t)$ into (6.23) to get

$$\begin{aligned}\frac{\partial A}{\partial t} &= \sum_{i=0}^{\infty} \Big[(\mu + \Gamma_u)(i+1)P_{i+1}(t) + \gamma q(t)P_{i-1}(t) \\ &\quad -(\mu + \Gamma_u)iP_i(t) - \gamma q(t)P_i(t)\Big]s^i \\ &= (\mu + \Gamma_u)\sum_{i=0}^{\infty} s^i(i+1)P_{i+1}(t) + \gamma q(t)\sum_{i=0}^{\infty} s^i P_{i-1}(t) \\ &\quad -(\mu + \Gamma_u)\sum_{i=0}^{\infty} s^i P_i(t) - \gamma q(t)\sum_{i=0}^{\infty} s^i P_i(t).\end{aligned}$$

We change indices, using $n = i+1$ in the first sum, and $m = i-1$ in the second sum to obtain

$$\begin{aligned}\frac{\partial A}{\partial t} &= (\mu+\Gamma_u)\sum_{n=1}^{\infty} s^{n-1}(n)P_n(t) + \gamma q(t)\sum_{m=0}^{\infty} s^{m+1}P_m(t) \\ &\quad -(\mu+\Gamma_u)\sum_{i=0}^{\infty} s^i P_i(t) - \gamma q(t)\sum_{i=0}^{\infty} s^i P_i(t).\end{aligned}$$

Use that $\dfrac{\partial A}{\partial s} = \displaystyle\sum_{i=0}^{\infty} P_i(t) i s^{i-1}$ and $A(s,t) = \displaystyle\sum_{i=0}^{\infty} P_i(t)s^i$, and make the appropriate substitutions and simplifications to get the closed form equation:

$$\frac{\partial A}{\partial t} = \gamma q(t)A(s-1) - (\mu+\Gamma_u)\frac{\partial A}{\partial s}(s-1). \tag{6.24}$$

Now we determine the closed form equation for $B(s,t)$. We have that

$$\frac{\partial B}{\partial t} = \sum_{j=0}^{\infty} \dot{Q}_j(t)s^j. \tag{6.25}$$

Substitute the expression for $\dot{Q}_j(t)$ into (6.25) to obtain

$$\begin{aligned}\frac{\partial B}{\partial t} &= \sum_{j=0}^{\infty}\Big[(\gamma+\Gamma_q)(j+1)Q_{j+1}(t) + \mu u(t)Q_{j-2}(t) \\ &\quad -(\gamma+\Gamma_q)jQ_j(t) - \mu u(t)Q_j(t)\Big]s^j \\ &= (\gamma+\Gamma_q)\sum_{j=0}^{\infty}(j+1)s^jQ_{j+1}(t) + \mu u(t)\sum_{j=0}^{\infty} s^jQ_{j-2}(t) \\ &\quad -(\gamma+\Gamma_q)\sum_{j=0}^{\infty} js^jQ_j(t) - \mu u(t)\sum_{j=0}^{\infty} s^jQ_j(t).\end{aligned}$$

Change indices using that $n = j+1$ in the first sum, and $p = j-2$ in the second sum to obtain:

$$\begin{aligned}\frac{\partial B}{\partial t} &= (\gamma+\Gamma_q)\sum_{n=1}^{\infty}(n)s^{n-1}Q_n(t) + \mu u(t)\sum_{p=0}^{\infty} s^{p+2}Q_p(t) \\ &\quad -(\gamma+\Gamma_q)\sum_{j=0}^{\infty} js^jQ_j(t) - \mu u(t)\sum_{j=0}^{\infty} s^jQ_j(t).\end{aligned}$$

Now we use that $\frac{\partial B}{\partial s} = \sum_{j=0}^{\infty} j s^{j-1} Q_j(t)$ and $B(s,t) = \sum_{j=0}^{\infty} Q_j(t) s^j$, and simplify to get the closed form equation:

$$\frac{dB}{dt} = \mu u(t) B(s^2 - 1) - (\gamma + \Gamma_q)\frac{\partial B}{\partial s}(s-1). \tag{6.26}$$

Rearranging (6.24) and (6.26) we have the system of closed form equations:

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial s}(\mu + \Gamma_u(t))(s-1) - A\gamma q(t)(s-1) = 0 \tag{6.27}$$

$$\frac{\partial B}{\partial t} + \frac{\partial B}{\partial s}(\gamma + \Gamma_q(t))(s-1) - B\mu u(t)(s^2-1) = 0. \tag{6.28}$$

This system of two partial differential equations can be solved using the method of characteristics. We need to find curves in the (t,s)-plane which reduce the equations in (6.27) and (6.28) to ODEs. Any curve in the (t,s)-plane can be described by the parametric equations: $t = t(w)$ and $s = s(w)$, where w is the parameter that measures the distance along the curve.

We first consider equation (6.27). To determine the initial condition, we substitute $t = 0$ into (6.21) to get $A(s,0) = s^{u(0)}$, which means that at time $t = 0$ there are exactly n active cells in the system. This implies that the curve begins, i.e, $w = 0$, when $s = s_0$, $t = 0$. In order to solve (6.27) using this method, we need to make the coordinate transformation from (s,t) to the new coordinates (s_0, w), where the new s_0 will be constant along the characteristics, and the new variable w will vary. The characteristic curve equations are:

$$\begin{aligned} \frac{dt}{dw} &= 1 \\ \frac{ds}{dw} &= (\mu + \Gamma_u(t))(s-1). \end{aligned}$$

Solving these, using the required initial conditions $t(s_0, 0) = 0$ and $s(s_0, 0) = s_0$ gives:

$$\begin{aligned} t(s_0, w) &= w \\ s(s_0, w) &= e^{\int_0^w (\mu + \Gamma_u(w))dw}(s_0 - 1) + 1. \end{aligned}$$

We have completed the coordinate transformation from (s,t) to (s_0, w). Substitute $s(s_0, w)$ and $t(s_0, w)$ into (6.27) to obtain the ODE

$$\frac{dA}{dw} - A\gamma q(w) e^{\int_0^w (\mu+\Gamma_u(w))dw}(s_0 - 1) = 0,$$

with solution

$$A(s_0, w) = (s_0)^{u(0)} \exp\left[\gamma(s_0 - 1)\int_0^w q(y) e^{\int_0^y (\mu+\Gamma_u(z))dz} dy\right]. \qquad (6.29)$$

Solve for s_0 and w in terms of s and t to obtain:

$$\begin{aligned} w(s,t) &= t \\ s_0(s,t) &= e^{-\int_0^w (\mu+\Gamma_u(w))dw}(s-1) + 1. \end{aligned}$$

Substitute these values for s_0 and w into (6.29) to get the solution to (6.27),

$$\begin{aligned} A(s,t) &= (e^{-\int_0^t (\mu+\Gamma_u(z))dz}(s-1) + 1)^{u(0)} \\ &\quad \times \exp\left[\gamma e^{-\int_0^t (\mu+\Gamma_u(z))dz}(s-1)\int_0^t q(y) e^{\int_0^y (\mu+\Gamma_u(z))dz} dy\right]. \end{aligned}$$

Now we consider (6.28). In this case, we solve for $B(s,t)$ with initial condition $B(s,0) = s^{q(0)}$ which corresponds to the curve that has initial point $s = s_0$, and $t = 0$. Again, we want to make the coordinate transformation from (s,t) to (s_0, w) in our characteristic equations. The characteristic curve equations are:

$$\begin{aligned} \frac{dt}{dw} &= 1 \\ \frac{ds}{dw} &= (\gamma + \Gamma_q(t))(s-1) \end{aligned}$$

with solutions

$$\begin{aligned} t(s_0, w) &= w \\ s(s_0, w) &= e^{\int_0^w (\gamma+\Gamma_q(w))dw}(s_0 - 1) + 1. \end{aligned}$$

We have again made the coordinate transformation from (s,t) to (s_0, w). Substitute $s(s_0, w)$ and $t(s_0, w)$ into (6.28) to obtain the ODE

$$\frac{dB}{dw} - B\mu N(w)\left[e^{2\int_0^w (\gamma+\Gamma_q(z))dz}(s_0 - 1)^2 + 2e^{\int_0^w (\gamma+\Gamma_q(z))dz}(s_0 - 1)\right] = 0,$$

with solution

$$B(s_0,w) = (s_0)^{q(0)} \exp\left[\mu(s_0-1)^2 \int_0^w u(y) e^{2\int_0^y(\gamma+\Gamma_q(z))dz} \right. \\ \left. +2\mu(s_0-1)\int_0^w u(y) e^{\int_0^y(\gamma+\Gamma_q(z))dz} dw\right]. \tag{6.30}$$

Again, solve for s_0 and w in terms of s and t to get:

$$\begin{aligned} w(s,t) &= t \\ s_0(s,t) &= e^{-\int_0^t(\gamma+\Gamma_q(t))dt}(s-1)+1. \end{aligned}$$

Substitute these values for s_0 and w into (6.30) to get the solution to (6.28),

$$\begin{aligned} B(s,t) = (e^{-\int_0^t(\gamma+\Gamma_q(z))dz}(s-1)+1)^{q(0)} \\ \exp\left[\mu(s-1)^2 e^{-2\int_0^t(\gamma+\Gamma_q(z))dz}\int_0^t u(y)e^{2\int_0^y(\gamma+\Gamma_q(z))dz}dy \right. \\ \left. +2\mu(s-1)e^{-\int_0^t(\gamma+\Gamma_q(z))dz}\int_0^t u(y)e^{\int_0^y(\gamma+\Gamma_q(z))dz}dy\right]. \end{aligned}$$

6.1.5 The Tumour Control Probability

We can now write the explicit expression for the TCP:

$$\begin{aligned} \text{TCP}(t) &= P_0(t)Q_0(t) \\ &= A(s=0,t)B(s=0,t) \\ &= (1-e^{-f(t)})^{u(0)}(1-e^{-g(t)})^{q(0)} \\ &\quad \exp\left[-\gamma e^{-f(t)}\int_0^t q(y)e^{f(y)}dy \right. \\ &\quad \left. +\mu e^{-2g(t)}\int_0^t u(y)e^{2g(y)}dy - 2\mu e^{-g(t)}\int_0^t u(y)e^{g(y)}dy\right] \end{aligned} \tag{6.31}$$

where

$$\begin{aligned} f(x) &= \int_0^x (\mu+\Gamma_u(z))dz, \\ &\text{and} \\ g(x) &= \int_0^x (\gamma+\Gamma_q(z))dz \end{aligned}$$

6.2 Active-Quiescent Model TCP Curves

In order to investigate the behaviour of the TCP (6.31) derived in the previous section, we look at graphs of the function plotted against time. In order to do this, we first determine realistic parameter values.

For an initial number of tumour cells, we use an estimate given in Wyatt et al. [28], which is 10^8 cells at diagnosis. Now that we have chosen an estimate for the initial number of tumour cells, we must divide these cells into two compartments: active and quiescent. Since there is no readily available data on the states of tumour cells, we assume half of the cells are in the active state, and half are in the quiescent state.

The parameter that is the most difficult to determine is γ, the transition rate from the quiescent to the active cell compartment. Prior to the recognition of this resting state, G_0 was included in the G_1 phase, which accounted for a highly variable length in the cell cycle. For the parameter γ, we use an estimate for the transition rate from the G_1 phase, to the S phase.

For the parameters A_1 and A_2, we use estimates for the α parameter in the LQ model since in both cases the parameters represent damage due to single-hit events. For A_1, the parameter for the active cell single-hit damage, we use a value of α for radiosensitive prostate tumour cells. For A_2, the single-hit damage parameter for the resting cell compartment, we use an α estimate for radioresistant prostate tumour cells. Similarly, for B, the term which represents damage due to two-hit events, we use an estimate for the β parameter in the LQ model for radiosensitive prostate tumour cells. These α and β estimates were taken from Leith et al. [14].

We summarize the values of the parameters used in Table 6.1.

Parameter	Value Used	Units	Reference
u_0	$10^8/2$	cells	[28]
q_0	$10^8/2$	cells	[28]
μ	0.0655	1/day	[25]
γ	0.0476	1/day	[2]
A_1	0.487	Gy^{-1}	[14]
A_2	0.155	Gy^{-1}	[14]
B	0.055	Gy^{-2}	[14]

Table 6.1: Parameter estimates used to generate plots of the active-quiescent TCP.

6.2.1 Constant Dose Rate

In this case, we assume the dose rate is a constant value of 2.75 Gy Day^{-1}. Figure 6.1 depicts a plot of the TCP as a function of time for this treatment schedule.

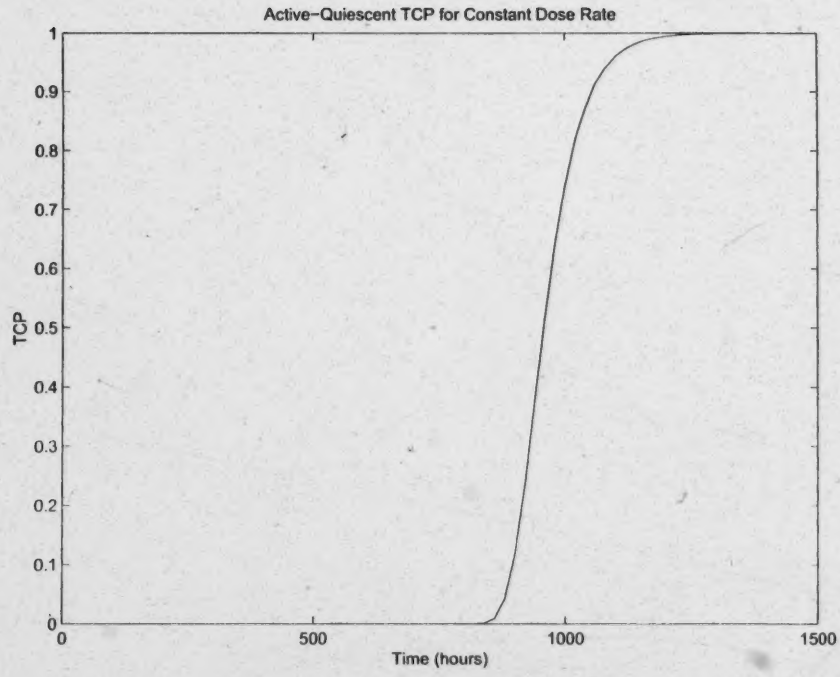

Figure 6.1: Plot of TCP versus Time with Constant Dose Rate.

The plot shows that at approximately 750 hours, or one month, the TCP begins to increase, which suggests this is when the treatment begins to have a positive effect. By 1200 hours, or 50 days, the TCP has reached its maximum value, which indicates a high probability of tumour eradication.

6.2.2 Time-Dependent Dose Rate

In this case, we look at a treatment schedule which consists of 25 fractions, with each fraction having a dose of 9 Gy. These fractions are administered each morning, for a total of 25 days. Figure 6.2 depicts the plot of the TCP as a function of time for this schedule. Despite the fact that the last fraction of radiation was given at approximately 600 hours, it is only after 500 hours that the TCP begins to increase. This increase is followed by drastic oscillations. This dynamical behaviour is not well understood and more research needs to be done. The TCP is numerically computed, and the algorithm is sensitive to the large initial values for the number of both active and resting cells.

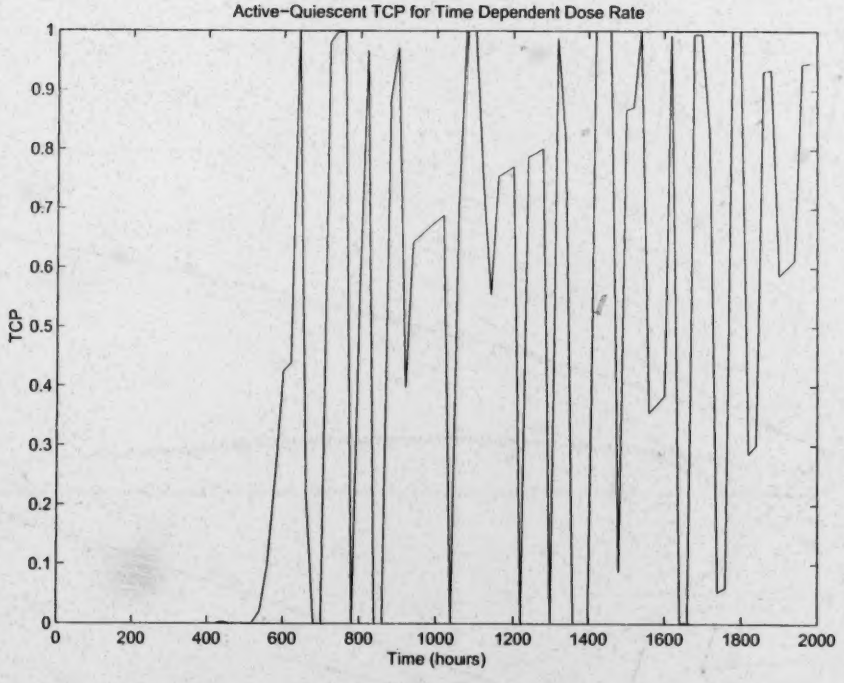

Figure 6.2: Plot of TCP versus Time with Time Dependent Dose Rate.

Chapter 7

Effects of Radiotherapy on the PSA Levels of Prostate Cancer Patients

When we began work on this thesis, we were interested in modeling the correlation between the effectiveness of a radiotherapy treatment and the level of prostate specific antigen (PSA) in a prostate cancer patient. Shortly after this work had begun, we obtained data which contained PSA levels for more than 700 prostate cancer patients throughout their respective treatments.

Newly diagnosed prostate cancer patients are usually treated with either radiation therapy, orchidectomy (a surgical procedure to remove the testes), or hormone therapy. After this initial treatment, patients are monitored to determine the success of the treatment. More specifically, it is important to know early if the cancer will recur. It is in this monitoring process where PSA is a helpful tool.

PSA is a serum biomarker produced by the prostate tissue, which can be easily measured from a blood sample. Although healthy men produce this antigen, prostate cancer patients exhibit higher levels of PSA. Also, PSA levels correspond with the severity of the cancer. Both surgery and radiation cause a decrease in PSA level, and if the treatment was effective, the PSA will remain at a lower level. However, if the treatment was not successful, as the cancer begins to regrow, the PSA level will increase accordingly. Most often, an increase in PSA level is detectable before the tumour is clinically detectable. Treatment failure is characterized by three consecutive increases in PSA level post treatment (American Society of Therapeutic Radiology and Oncology).

In this chapter, we review the literature that motivated this work, include some information regarding the available data acquired from the Cross Cancer Institute (CCI), and discuss future work.

7.1 The Model of Dayananda, Taylor and Whiting

In [7], Dayananda, Taylor, and Whiting use a deterministic model, previously presented by Kaplan et al. in [10], as a foundation for a stochastic model for the impact of radiation on the PSA level.

In the deterministic model, $X(t)$ denotes the PSA level at time t, and the PSA increase caused by tumour growth is defined as $\alpha X(t)$. Also, assume that treatment is applied at time $t = 0$, and that the PSA decrease due to radiation therapy is ke^{-at}, where k represents the intensity of the treatment, and a represents the intrinsic decay in tumour cells. Then the differential equation for the change of PSA level with respect to time is given by

$$\frac{dX}{dt} = \alpha X - ke^{-at}. \tag{7.1}$$

With the assumption that at time $t = 0$, the PSA level was m, or $X(0) = m$, the solution to (7.1) is

$$X(t) = \left[m - \frac{k}{a+\alpha}\right] e^{\alpha t} + \left[\frac{k}{a+\alpha}\right] e^{-at}. \tag{7.2}$$

Based on the biological assumptions, from this solution the success of the therapy can be determined. If $m < \frac{k}{a+\alpha}$ then the treatment was successful, and no relapse occurs. However, in this case, $X(t)$ decreases to zero, and then becomes negative which is not biologically feasible. If $\frac{k}{a+\alpha} < m < \frac{k}{\alpha}$, then $X(t)$ has a minimum, so after the initial decline in $X(t)$, a relapse occurs. Lastly, in the case where $m > \frac{k}{\alpha}$, the treatment was not successful, and a relapse occurs immediately post-treatment.

In this deterministic model, the success of a given treatment is determined by the initial value m of $X(t)$.

In order to derive the stochastic model, Dayananda et al. assume that $X(t)$ is a discrete random variable which takes nonnegative integer values. Then the change in $X(t)$ can be written as a birth-death process, where our interval of interest is defined as $[t, t + \delta t]$.

$$P\{X(t, t+\delta t) = n+1 | X(t) = n\} = \alpha n \delta t \tag{7.3}$$

$$P\{X(t, t+\delta t) = n-1 | X(t) = n\} = ke^{-at}\delta t n \tag{7.4}$$

We define the probability that $X(t) = n$ as $p_n(t)$, and then the difference-differential

equations for this process are as follows:

$$\frac{dp_0(t)}{dt} = p_1(t)ke^{-at} \tag{7.5}$$

and for $n > 0$

$$\frac{dp_n(t)}{dt} = -(\alpha n + ke^{-at})p_n(t) + \alpha(n-1)p_{n-1}(t) + ke^{-at}(n+1)p_{n+1}(t). \tag{7.6}$$

Using the standard generating function $G(z,t)$, the following PDE is derived:

$$\frac{\partial G}{\partial t} = \alpha z(z-1)\frac{\partial G}{\partial z} + ke^{-at}\left(\frac{1-z}{z}\right)(G - p_0(t)). \tag{7.7}$$

As in the deterministic case, we assume that $X(0) = m$ which corresponds with the boundary condition

$$G(z,0) = z^m. \tag{7.8}$$

The solution to (7.6) is, for $n \geq 1$,

$$p_n(t) = e^{-u(t)} \sum_{r=1}^{m} \binom{n-1}{r-1} (1 - e^{-r\alpha t}) \frac{u(t)^{m-r}}{(m-r)!}, \tag{7.9}$$

where $u(t) = \frac{k}{a+\alpha}(1 - e^{-(a+\alpha)t})$.

Using data for PSA level profiles of prostate cancer patients, Dayananda et al compare the fit of both the deterministic model and the stochastic model. Covariates depending on an individual patient, the stage and grade of the cancer, and the treatment characteristics are hypothesized to have a significant influence on the values of the parameters a, α, and k.

The only obvious advantage of the stochastic model versus the deterministic model is that the PSA level will never become negative in the stochastic case. The assumption that the PSA level takes only discrete values hinders the model's accuracy, whereas the deterministic model has the capability to predict all possible PSA values. Also, both models presented in [7] assume that the treatment is administered at time $t = 0$, which prevents the model from being able to track the PSA levels throughout the therapy, which could in reality extend over several weeks or months.

Both the stochastic model and the deterministic model were fitted to data for the PSA levels of prostate cancer patients, and the parameter values obtained were $a = 2.17\text{yr}^{-1}$, $\alpha = 2.83\text{yr}^{-1}$, and $k = 60\text{yr}^{-1}$ [6]. No error bound information was provided in this paper.

7.2 The Data

In February 2004, we made contact with Dr. David McGowan, at the Cross Cancer Institute. In 1988, he developed a database to record prostate cancer patient data. Now the database contains information for 771 prostate cancer patients of the CCI throughout the course of their respective treatments. The database includes information such as the grade of cancer, patients respective treatments, their PSA levels throughout the course of the treatment, and follow-up information after treatment had been completed.

The prostate cancer patients of the Cross Cancer Institute (CCI) were treated using either one of, or a combination of, radiation therapy, orchidectomy, and hormone therapy. We were interested in studying the case where patients were treated exclusively with radiation therapy, so the first step was to determine which group of patients fell into this category. Out of the 771 total patients, 175 had received an orchidectomy or hormone therapy (either exclusively, or in combination with radiation therapy).

Another consideration was the PSA testing method used. Until March of 1999, the CCI used the Hybritech PSA testing method. During this month, they began to use a different PSA measuring system, called the Roche Assay method. Each method used different test reagents, which resulted in slightly different PSA readings. Out of the 596 patients who were treated with only radiation therapy, 362 were treated when the Hybritech system was in use, and only 6 were treated when the Roche system was in use. We decided to use only the data from those treated prior to March 1999. The last consideration before working with the data was to eliminate patients who had fewer than 3 PSA-level entries, which was the chosen minimum number of points to perform the data fitting, as well as the patients whose data contained errors, such as an invalid date. After these patients were identified, and removed from the list, there were a total of 258 patients who satisfied the required criteria.

7.3 Data Fitting to Deterministic Model

Based on our data, we critically discuss Kaplan's deterministic model (7.1). As we fitted Kaplan's model to our data, we found that many biologically realistic properties were neglected in the model. This in turn motivated us to study a more detailed model in Chapters 4-6.

Using the data for 258 prostate cancer patients who had undergone only radiation therapy, we were able to determine the parameters for the deterministic model (7.2). In order to do this, we used a least squares method to fit the model to each individual patient, and after doing this, took the average values over the data set of the three parameters a, α, and k. The average values of these parameters for our

data, with the respective standard deviations, as well as the parameter values found by Dayananda et al., who used prostate cancer data from the University of Michigan Cancer Center, are given in the table below.

Parameter	Average Value Found ($year^{-1}$)	Standard Deviation ($year^{-1}$)	Dayananda's Value ($year^{-1}$)
a	2.9406	7.4937	2.17
α	1.1518	2.1511	2.83
k	66.7093	129.7624	60

Table 7.1: A comparison of the Kaplan deterministic model parameters obtained by us using prostate cancer data from the CCI, and those values obtained by Dayananda et al. using prostate cancer data from the University of Michigan Cancer Center.

7.3.1 Critical Analysis of Kaplan's Deterministic Model

In some cases, the fit appeared to be quite good, and the parameter estimates found by Dayananda et al. were accurate. We show two such cases in Figures (7.1) and (7.2) below.

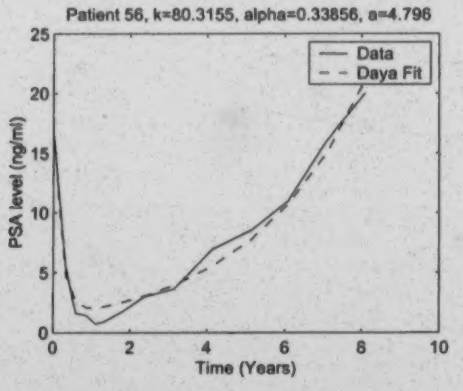

Figure 7.1: Fit for patient 56. $k = 80.3155$, $\alpha = 0.3386$, $a = 4.7960$, and $m = 8.2$.

PSA Decreases to Negative Values

In the case where the treatment is successful, the model predicts that the PSA will continue to decline with time, predicting negative PSA values in finite time. Realistically, if the treatment is successful, the PSA level should decrease with time

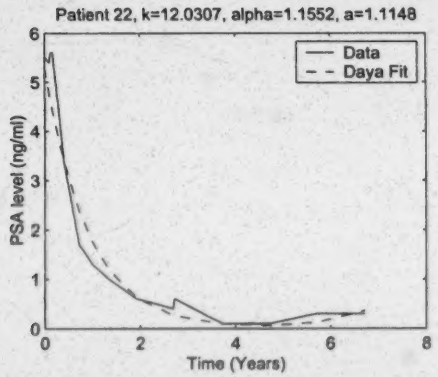

Figure 7.2: Fit for patient 22. $k = 28.8867$, $\alpha = 1.7760$, $a = 1.7461$, and $m = 8.2$.

until it reaches a healthy base level. Once this base level has been reached, the PSA should remain at this constant lower healthy level. An example of the prediction of negative PSA values can be seen in the Figure 7.3, where the value of PSA after 2.6 years is -0.0786 ng/ml.

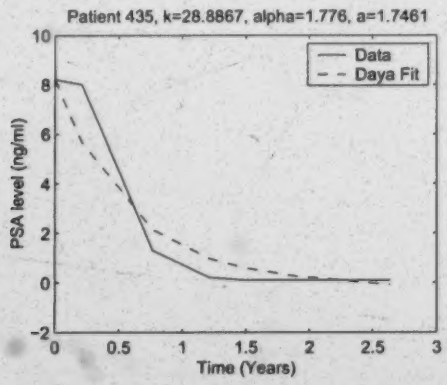

Figure 7.3: Fit for patient 435. $k = 28.8867$, $\alpha = 1.7760$, $a = 1.7461$, and $m = 8.2$. Notice that Kaplan's model predicts negative values.

No Initial Rise in PSA Levels

In many cases, the data shows an initial rise in the PSA level, before decreasing. The model does not have the capacity to predict this initial increase. Figure 7.4 shows a case where there is an initial increase with a plot of the deterministic model fitted to this data.

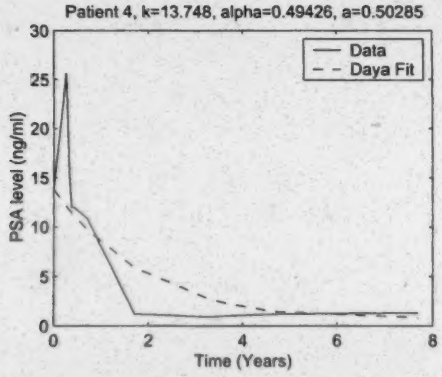

Figure 7.4: Fit for patient 4. $k = 13.7480$, $\alpha = 0.4943$, $a = 0.5029$, and $m = 13.8$. Notice the initial rise in PSA level.

Treatment Assumed to be Instantaneous

In this model, it is assumed that the treatment is applied at time $t = 0$. Also, it is assumed that the PSA level just prior to treatment is m, which is written as $X(0) = m$. This implies that the treatment is instantaneous, which is unrealistic. Radiation therapy schedules usually last weeks, and the dose is given in daily fractions. In the data, there are cases in which the treatment appears initially successful, followed by a recurrence, followed by a decrease in PSA. This is probably a result of fractionated therapy, which most of the patients received. (It is not the case that treatment was applied only at time $t = 0$.) An example of an instance where the model fails to describe a decrease in PSA is seen in Figure 7.5.

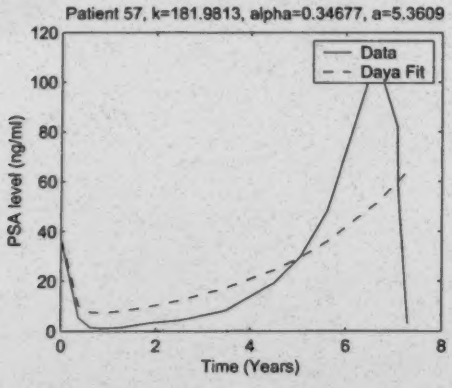

Figure 7.5: Fit for patient 57. $k = 181.9813$, $\alpha = 0.3468$, $a = 5.3609$, and $m = 37.0$. At 6 years, there is decrease in PSA, probably due to a second treatment.

Negative a and k Values

When fitting the deterministic model to our data, there were some cases where α or a were negative. In the model derivation, it is assumed that all parameters are nonnegative, and the analysis of the model is carried out using this assumption. Due to this, we are unable to apply the theoretical results to our data. The parameter α represents the rate at which the PSA level is influenced by the tumour. In the case that α is negative, it means only that the PSA is decreasing, which presents no problems. The parameter a represents the decay of the therapy effects. In the case that a is negative, this means that the therapy benefits to the tumour increase exponentially with time. In Figures 7.6 and 7.7, we show a case where α is negative, as well as a case where a is negative.

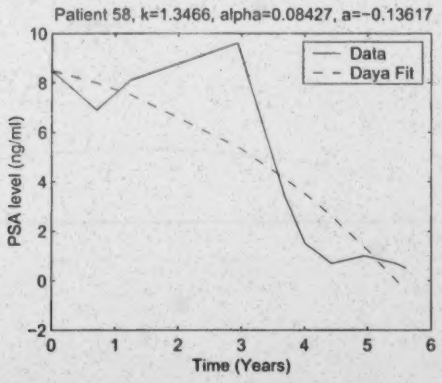

Figure 7.6: Fit for patient 58. $k = 1.3466$, $\alpha = 0.0843$, $a = -0.1362$, and $m = 8.5$. Notice that the a value is negative.

7.4 Development of a New Model

As shown in the previous section, the deterministic model (7.1) is not biologically realistic. In order to improve this model, it is important to include dose rate dependance so it is possible to monitor the cumulative effects of the treatment, regardless of the treatment schedule. Also, although it is usually assumed that only viable cells secrete PSA, we believe that the secretion difference in active and resting cells should also be considered, as this could have an impact on system dynamics. The model from Chapter 4-6 needs to be extended to include PSA dynamics. Then, a new fit of this model to our CCI prostate cancer data set should be done.

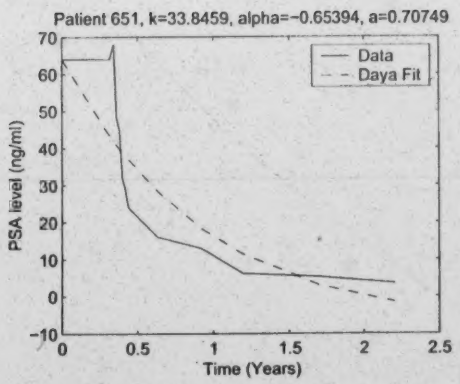

Figure 7.7: Fit for patient 651. $k = 33.8459$, $\alpha = -0.6539$, $a = 0.7075$, and $m = 64.0$. Notice that the α value is negative.

Chapter 8

Discussion

In this thesis, I mathematically describe the radiation treatment of cancer cells, beginning at the cellular level. Using this mathematical description, which consisted of a system of two ODEs, I was able to subsequently derive an expression for the TCP, which is useful in determining the outcome of a specific treatment schedule.

Initially, my motivation came from examining the relationship between the radiation treatment of prostate cancer tumours, and the change in PSA levels. I applied an existing model of Kaplan et al. to a data set obtained from the CCI, which consisted of PSA levels for 258 prostate cancer patients throughout the course of their respective radiotherapy treatments. The shortcomings of Kaplans model motivated me to further investigate the effects of radiotherapy on cancer cells. These effects have been studied extensively for many years. The first widely recognized mathematical model of this process came only in 1966, when the LQ model was first developed. Many later mathematical models of the radiation treatment of cancer have considered an inhomogeneous cell population of varying radiosensitivities, without classifying the mechanism behind these variations. It is only recently that the quiescent, or G_0, phase was recognized as a cellular state which the cell can enter from the classical four phase cell cycle. It has been shown that cells in this quiescent state are less sensitive to radiation than cells which are proliferating. For this reason, I felt it was important to consider this resting state when developing our model. I proceeded to divide the cell population into two compartments: a quiescent compartment G_0, and an active compartment, which includes the G_1, S, G_2, and M phases of the cell cycle. The derivation of the active-quiescent radiation model began from first principles, where I considered how radiation affects a single cell. Once cell specific target sites that could be damaged via energy deposits were established, the model was extended to groups of cells in the two respective compartments. The result of this derivation was a system of two ODEs, which includes the effects of a time-dependent radiation dose rate, and incorporates the dynamics of the active-quiescent cell cycle (see 4.13).

Once the active-quiescent radiation model was established, I was interested in studying the effects of the two parameters which governed a cells movement through the quiescent and active phases. The first parameter, μ, describes the proliferation rate, and the second parameter, γ, describes the transition rate from the quiescent to the active cell compartment. Using perturbation analysis, I found that the relative sizes of these parameters have a significant effect on the solutions of the active-quiescent system. When μ and γ are both small, I obtain a modified linear-quadratic model. When γ is large and μ is small, I found that the one-hit event damage on resting cells has no effect, while when μ is large and γ is small, the effect of radiation on the active cells does not contribute to the leading order system behaviour.

Further, I was interested in comparing the active-quiescent model with the LQ model, which is the standard model used when modeling the effects of radiation. The size of the ratio of the two parameters in the LQ model, referred to as α/β ratio, has been hypothesized to correlate with the length of the classical four phase cell cycle. My comparison of these two models led to the confirmation that a large α/β ratio corresponds to a fast cell cycle, and a smaller α/β ratio corresponds with a slow cell cycle. I hypothesize that a large α/β ratio indicates a significant quiescent compartment.

My next goal, following the model analysis, was to extend the results of Zaider and Minerbo by deriving an expression for the active-quiescent TCP. To do this, I follow a similar method as that used in [29]. The first step was to extend my model to a nonlinear birth-death process (see 6.7, and 6.8). Following this, I was able to solve this system of infinitely many differential equations using generating functions. Once the solution was obtained, I found an explicit expression for the active-quiescent TCP, or the probability that there are zero tumour cells at time t. This expression can be used to analyze a variety of treatment plans of varying dose rates, number of fractions, and overall treatment time.

8.1 Further Studies

In order to extend the model presented in this thesis, I would like to investigate the effects of the active-quiescent cell cycle on the PSA level during radiotherapy treatment of prostate cancer. This could be accomplished by adding a third equation to the active-quiescent model which determines the PSA level during treatment. This three-ODE model could then be fitted to the CCI data set to determine the effects of the quiescent phase on cell PSA secretion.

Bibliography

[1] G.W. Barendsen. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *International Journal of Radiation, Oncology, Biology, and Physics*, 8:1981–1997, 1982.

[2] B. Basse, B.C. Baguley, E.S. Marshall, W.R. Joseph, B. van Brunt, G. Wake, and D.J.N. Wall. A mathematical model for analysis of the cell cycle in human tumour. *Journal of Mathematical Biology*, 47:295–312, 2002.

[3] F.M. Buffa, J.D. Fenwick, and A.E. Nahum. An analysis of the relationship between radiosensitivity and volume effects in tumor control probability modeling. *Medical Physics*, 27:1258–1265, 2000.

[4] M. Carlone. *Determining the α/β Ratio for Prostate Cancer Using Clinically Measured Dose Response Data*. PhD thesis, Carleton University, Canada, 2004.

[5] K.H. Chadwick and H.P. Leenhouts. A molecular theory of cell survival. *Physics in Medicine and Biology*, 18:78–87, 1973.

[6] P.W.A. Dayananda, J.T. Kemper, and M.M. Shvartsman. A stochastic model for prostate-specific antigen levels. *Mathematical Bioscience*, 190:113–126, 2004.

[7] P.W.A. Dayananda, J.M.G. Taylor, and D.G. Whiting. Prostate cancer: progression of prostate-specific antigen after external beam irradiation. *Mathematical Biosciences*, 182:127–134, 2003.

[8] P. Friedl and E.B. Bröcker. The biology of cell locomotion within three dimensional extracellular matrix. *Cell Motility Life Science*, 57:41–64, 2000.

[9] M. Goitein, A. Niemierko, and P. Okunieff. The probability of controlling an inhomogeneously irradiated tumour: a strategem for improving tumor control through partial boosting. *British Journal of Radiology*, S1:25–39, 1997.

[10] I.D. Kaplan, M.A. Cox, and M.A. Bagshaw. A model of prostatic carcinoma tumor kinetics based on prostate specific antigen levels after radiation therapy. *Cancer*, 68:400–405, 1991.

[11] A.M. Kellerer and H.H. Rossi. RBE and the primary mechanism of radiation action. *Radiation Research*, 47:15–34, 1971.

[12] A.M. Kellerer and H.H. Rossi. Some characteristics of tumour control probability for heterogeneous tumours. *Physics in Medicine and Biology*, 41:2125–2133, 1996.

[13] D.G. Kendall. On the generalized "birth-and-death" process. *Annals of Mathematical Statistics*, 19:1–15, 1948.

[14] J.T. Leith, L. Quaranto, G. Padfield, S. Michelson, and A. Hercbergs. Radiobiological studies of PC-3 and DU-145 human prostate cancer cells: X-ray sensitivity in vitro and hypoxic fractions of xenografted tumors in vivo. *International Journal of Radiation Oncology, Biology and Physics*, 25:283–287, 1993.

[15] J.D. Logan. *Applied Mathematics*. Jon Wiley and Sons, New York, 1997.

[16] F. Macdonald and C.H.J. Ford. *The Molecular Biology of Cancer*. BIOS Scientific Publishers Limited, Oxford, 1997.

[17] J. Mendelsohn, P.M. Howley, M.A. Israel, and L.A. Liotta. *The Molecular Basis of Cancer*. W.B. Saunders Company, Philadelphia, 2001.

[18] A.E. Nahum and D.M. Tait. Maximising local control by customised dose prescription for pelvic tumours. In *Advanced Radiation Therapy: Tumour Response Monitoring and Treatment Planning*, pages 425–431. Springer-Verlag, 1992.

[19] A. Niemierko and M. Goitein. Implementation of a model for estimating tumor control probability for an inhomogeneously irradiated tumor. *Radiotherapy and Oncology*, 29:140–147, 1993.

[20] D.M. Prescott and A.S. Flexer. *Cancer: The Misguided Cell*. Sinauer Associates Inc., Massachusetts, 1982.

[21] R.K. Sachs, P. Hahnfeld, and D.J. Brenner. The link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. *International Journal of Radiation Biology*, 72:351–374, 1997.

[22] R.K. Sachs, L.R. Hlatky, and P. Hahnfeldt. Simple ODE models of tumor growth and anti-angiogenic or radiation treatment. *Mathematical and Computer Modelling*, 33:1297–1305, 2001.

[23] W.K. Sinclair. The shape of radiation survival curves of mammalian cells cultured in vitro. *Biophysical Aspects of Radiation Quality, International Atomic Energy Agency, Technical Reports Series*, 58:21–43, 1966.

[24] W.K. Sinclair. Cyclic X-ray responses in mammalian cells in vitro. *Radiation Research*, 33:620–643, 1968.

[25] K.R. Swanson, L.D. True, D.W. Lin, K.R. Buhler, R. Vessella, and J.D. Murray. A quantitative model for the dynamics of serum prostate-specific antigen as a marker for cancerous growth. *American Journal of Pathology*, 158:2195–2199, 2001.

[26] A. Swierniak, A. Polanski, and M. Kimmel. Optimal control problems arising in cell-cycle-specific cancer chemotherapy. *Cell Proliferation*, 29:117–139, 1996.

[27] S. Webb and A.E. Nahum. A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distributioins of dose and clonogenic cell density. *Physics in Medicine and Biology*, 38:653–666, 1993.

[28] R.M. Wyatt, A.H. Beddoe, and R.G. Dale. The effects of delays in radiotherapy treatment on tumour control. *Physics in Medicine and Biology*, 48:139–155, 2003.

[29] M. Zaider and G.N. Minerbo. Tumour control probability: a formulation applicable to any temporal protocol of dose delivery. *Physics in Medicine and Biology*, 45:279–293, 2000.